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Risk factors of hepatocellular carcinoma in non-alcoholic fatty liver disease: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: This study aimed to systematically review and quantitatively synthesize the existing evidence to better identify the high-risk population of hepatocellular carcinoma (HCC) in nonalcoholic fatty liver disease (NAFLD).

MATERIALS AND METHODS: We searched databases including MEDLINE, EMBASE, Web of Science, Cochrane Library, and ClinicalTrials.gov up to February 2023. The meta-analysis was performed using RevMan5.3 software, and we calculated the estimated combined effect using inverse variance weighting of OR. I2 statistics were used to quantify the inter-study heterogeneity. Funnel plots and Egger test were used to assess publication bias, and sensitivity analysis was carried out through the transformation effect model or the removal of literature one by one.

RESULTS: Finally, 29 articles were included in the study, which involved a total of 726,656 patients with NAFLD. A total of 15 major risk factors were evaluated. Statistically significant risk factors were: advanced liver fibrosis (OR=6.40), diabetes (OR=2.38), obesity (OR=1.46), hypertension (OR=1.75), older age (OR=3.57), male (OR=2.45), alcohol intake (OR=2.98), smoking (OR=1.44), PNPLA3 genotype variation (OR=1.76), elevated liver enzymes (OR=2.92), low platelet counts (OR=4.61), and low albumin levels (OR=2.11).

CONCLUSIONS: Our results showed that advanced liver fibrosis, diabetes, obesity, hypertension, older age, male, alcohol intake, smoking, PNPLA3 genotype variation, elevated liver enzymes, low platelet counts, and low albumin levels were all significant risk factors for HCC in NAFLD. However, dyslipidemia was not found to be a risk factor. Further exploration is needed to confirm whether Hispanic ethnicity and high ferritin levels are also risk factors.

Key Words:
Non-alcoholic fatty liver disease, Hepatocellular carcinoma, Risk factors, Systematic review.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a growing concern worldwide, encompassing a range of disorders, including nonalcoholic simple fatty liver disease, nonalcoholic steatohepatitis and associated cirrhosis, and hepatocellular carcinoma (HCC)[1]. High-fat and high-sugar diets have contributed to the increasing prevalence of NAFLD, affecting approximately one-quarter of the world's population[1,2]. Estimates suggest that around one-quarter of the world's population has NAFLD[1], with projections indicating a potential 56% increase in incidence over the next decade[3]. HCC, the most common primary liver cancer, has traditionally been associated with hepatitis virus and alcohol, primarily in individuals with liver cirrhosis[4-6]. However, recent studies[7-10] have shown that NAFLD can also progress to cirrhosis and HCC, with potentially greater harm than previously understood. Misdiagnosis and labeling of NAFLD-associated cirrhosis as "cryptogenic cirrhosis" can delay recognition of the increased risk of HCC in NAFLD. Studies[7-10] suggest that NAFLD-associated HCC may be the main category of non-cirrhotic HCC, with a more subtle course, larger tumor, and poorer prognosis.

The estimated incidence of HCC in patients with NAFLD is 0.44/1000 person-years, with NAFLD-related cirrhosis at 9-26/1000 person-years[7]. Given the significant number of individuals affected by NAFLD and the increasing global cancer

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rate, it is crucial to raise awareness and identify high-risk subgroups of HCC among NAFLD patients[11]. In 2022, Chen et al[12] conducted a meta-analysis examining the relationship between diabetes, overweight/obesity, hypertension, dyslipidemia, and the incidence of NAFLD-related HCC. They concluded that diabetes and overweight/obesity were strong risk factors, while hypertension and dyslipidemia had no correlation. However, their study only included 8 cohort studies, and the discussion of risk factors was not comprehensive. Currently, there are still issues regarding inadequate quality of evidence, incomplete reports, and wide variations in research results. This study aims to conduct a comprehensive systematic review and meta-analysis to thoroughly analyze the risk factors of HCC in the NAFLD population, providing guidance for clinical diagnosis, treatment, and community prevention.

Materials and Methods

Search Strategy and Selection Criteria

In March 2021, a systematic search was conducted in relevant databases, including MEDLINE, EMBASE, Web of Science, the Cochrane Library, Clinical Trials.gov, etc., with no date or language restrictions to identify potentially relevant studies. Additionally, manual searches of the reference lists of potentially relevant papers and previous review articles were conducted. Medical subject headings and free text terms for NAFLD, risk factors, and HCC were used, and the search strategies of MEDLINE, EMBASE, and Web of Science are shown in **Supplementary Table I**. The search was updated in February 2023 to ensure the inclusion of the latest relevant studies.

After merging and eliminating duplicates from the search results of five databases, we conducted an eligibility assessment. The diagnosis of NAFLD and HCC was based on clinical, imaging, or liver biopsy results, and the study types were limited to cohort studies or case-control studies. We ensured that all included papers were of high quality and provided odds ratios (OR) (or data that could be converted to OR) and 95% confidence intervals (CI). We excluded case reports, reviews, guidelines, and animal experiments, as well as studies with incomplete data or without full text. The evaluation was carried out in compliance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (**Supplementary Table II**)[13].

Data Extraction and Literature Quality Evaluation

The screening of results was conducted independently by two researchers in strict accordance with the established criteria. In cases where different opinions were encountered, a third person was consulted to evaluate the study. The researchers then discussed together and consulted the full text for further review. Information was extracted from the studies, including author, year of publication, country, number of patients diagnosed with NAFLD, number of HCC cases, data source, duration of follow-up, risk factors exposed, and OR value.

The risk of bias was assessed independently by two authors using the Newcastle-Ottawa Scale (NOS), which evaluated studies based on study group selection, group comparability, and the results of exposure/outcome determination scores. Studies with scores ≥6 were considered to be of high quality.

Statistical Analysis

We performed a meta-analysis using RevMan 5.3 software version (Review Manager Web, The Cochrane Collaboration, Copenhagen, Denmark) and estimated the pooled effect using inverse variance weighting of OR. The inter-study heterogeneity was quantified using I^2 statistics, and the significance of heterogeneity was tested using Cochran's Q test (p threshold=0.05). A fixed effect model was utilized when $I^2 \leq 50\%$, and a random effects model was utilized when $I^2 > 50\%$. We assessed publication bias using funnel plots and the Egger test implemented in Stata 15.1 software (StataCorp LP, College Station, TX, USA). A symmetrical funnel plot and $p > 0.05$ indicated no significant publication bias, while an asymmetrical funnel plot and $p < 0.05$ indicated a certain publication bias. To evaluate the stability of the study conclusions, we used the Trim and Fill analysis for meta-analysis and comparison with the results of the original study. Furthermore, we conducted sensitivity analysis through the transformation effect model or the removal of literature one by one.

Results

During the two rounds of search, a total of 16,874 articles were obtained, and after screening and selection, 29 articles[14-42] were included in the meta-analysis (Figure 1). Of these, 23[14-16,18,20-

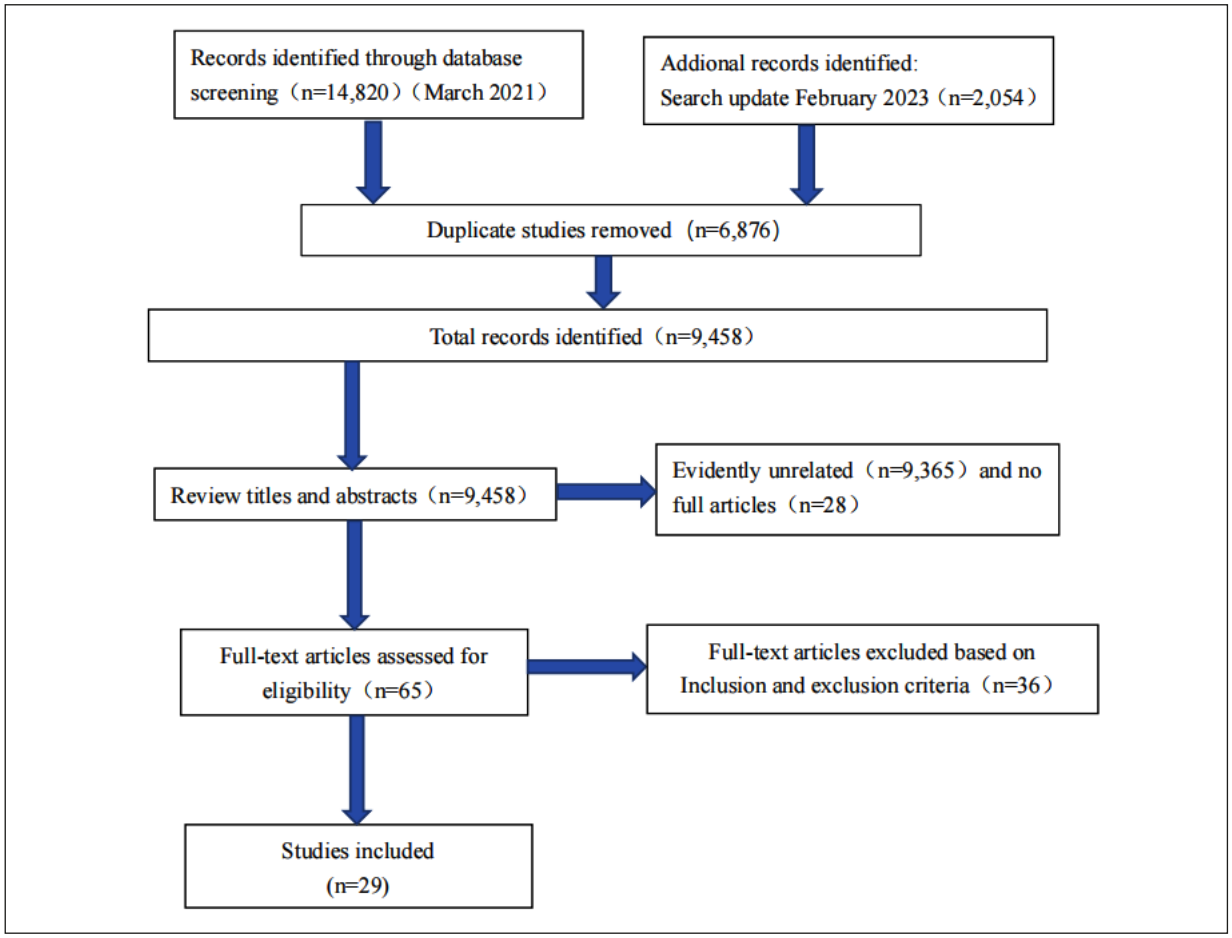

Figure 1. PRISMA diagram of study selection.

[28,31,32,35,37-42] were cohort studies and 7[17,19,29,30,33,34,36] were case-control studies, including a total of 726,656 patients with NAFLD. The follow-up time ranged from 21 months to 111.6 months, and the number of patients with HCC ranged from 7 to 1,310 during the follow-up period. One study by Yang et al[14] included two cohorts (the experimental group and the validation group). The entirety of the studies that were included exhibited high quality. A thorough review was carried out on the 15 risk factors: advanced liver fibrosis, diabetes, obesity, hypertension, dyslipidemia, older age, male, Hispanic ethnicity, alcohol intake, smoking, *PNPLA3* genotype variation, elevated liver enzymes, low platelet, low albumin, high ferritin (**Supplementary Table III**).

Advanced Liver Fibrosis

Twelve studies[15,16,18,21,22,25,27,29,32,37,39,41] have shown that advanced liver fibrosis has a significant impact on individuals with NAFLD, with a pooled OR of 6.40, 95% CI (3.89-10.53), $p<0.00001$, although with moderate heterogeneity ($I^2=63\%$) (Figure 2A). The funnel plot indicated a certain publication bias (Egger test $p=0.000$) (**Supplementary Figure 1A**). After including six virtual studies through the Trim and Fill analysis, the Improved odds ratio (IOR) was 6.156, $p=0.000$, indicating that the research conclusions were consistent (**Supplementary Figure 2A**). Sensitivity analysis was conducted using the method of eliminating one study at a time. We deleted the study that caused the greatest heterogeneity (Donati et al[29] 2017) and adopted a fixed-effect model for analysis. The pooled OR was 3.49, 95% CI (2.71-4.49), $p<0.00001$ (**Supplementary Figure 3A**), and the results were robust.

Diabetes

Individuals with NAFLD and diabetes have a significantly higher risk of developing HCC than those without diabetes, with a combined

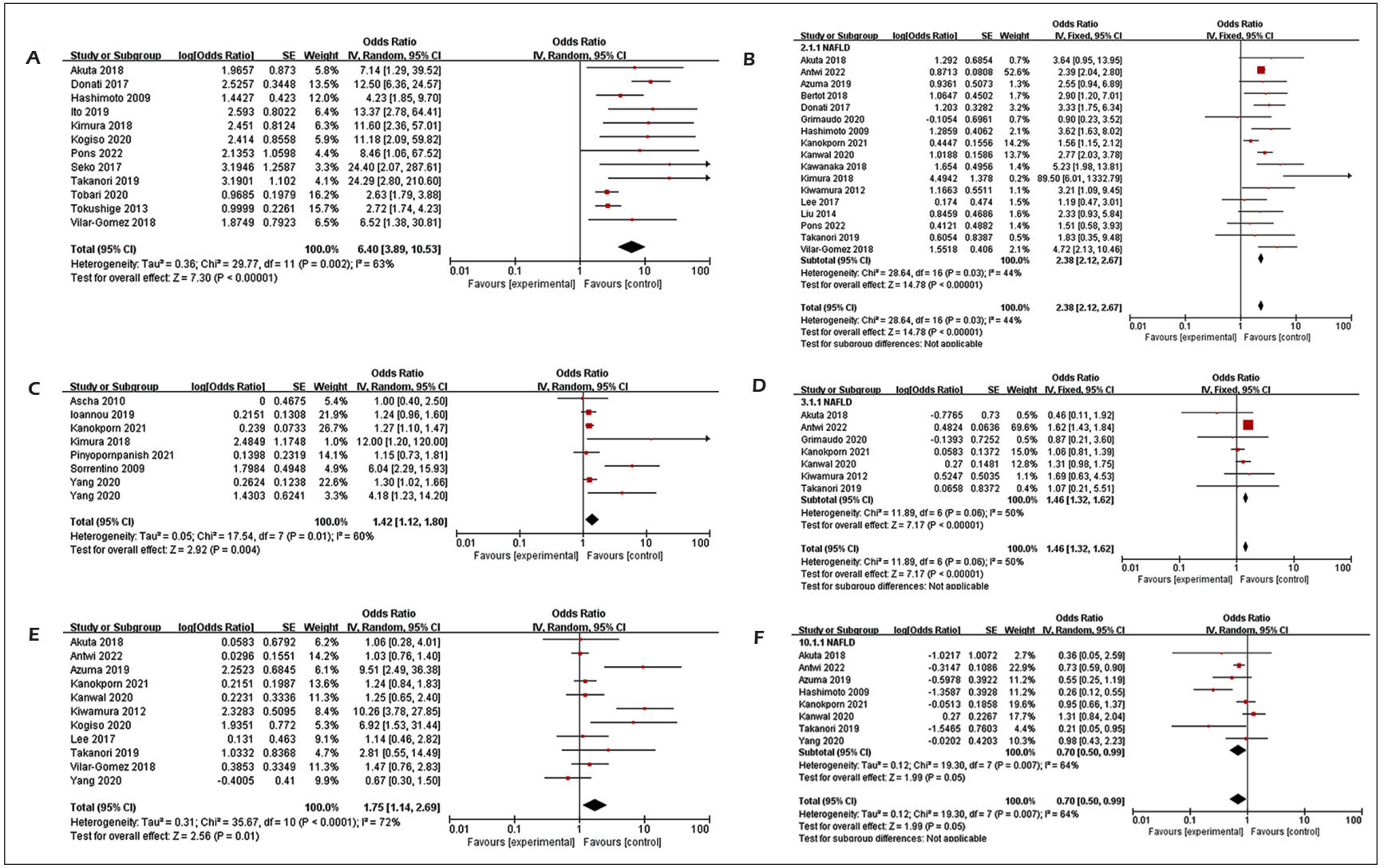

Figure 2. Forest plots depicting (**A**) advanced liver fibrosis; (**B**) diabetes; (**C**) diabetes in cirrhosis patients; (**D**) overweight/obesity; (**E**) hypertension; (**F**) dyslipidemia.

OR of 2.38 (95% CI=2.12-2.67). There was no significant heterogeneity observed, with an I^2 of 44% (Figure 2B). The funnel plot was relatively symmetrical (Egger test p=0.138). There were eight studies[14,17,22,26,31,34,38] that included patients with NAFLD cirrhosis. The pooled OR was 1.42 and statistically significant (p=0.004), moderately heterogeneous (I^2=60%) (Figure 2C), and there was a certain publication bias (Egger test p=0.034) (**Supplementary Figure 1B-C**). When one virtual study was included through the Trim and Fill analysis, the IOR was 1.713, p=0.001 (**Supplementary Figure 2B**). Sensitivity analysis showed that Sorrentino et al[17] and Pinyopornpanish et al[34] were heterogeneous sources (two case-control studies), and the pooled OR after exclusion was 1.32 (**Supplementary Figure 3B**). Consequently, the result was relatively robust. The influence of diabetes on patients with NAFLD cirrhosis with respect to the development of HCC is relatively small.

Overweight/Obesity

Three studies[32,41,42] defined overweight as having a BMI≥25, while two studies[24,28] defined obesity as a BMI of more than 30, and two studies[34,36] collected database-coded obesity information. After combining the results, the pooled OR was 1.46, with a 95% CI of (1.32-1.62). This was statistically significant (p<0.00001), with insignificant heterogeneity (I^2=50%) (Figure 2D). The absence of publication bias was indicated by both the funnel plot and the Egger test (p=0.616) (**Supplementary Figure 1D**). Sensitivity analysis with a different effect model showed that the result remained statistically significant [OR=1.30, 95% CI (1.03-1.64), p=0.03] (**Supplementary Figure 3C**).

Hypertension

Eleven studies[14,20,21,23-25,32-34,36,39] reported the association between hypertension and the occurrence of HCC in NAFLD patients, with a pooled OR of 1.75 (95% CI=1.14-2.69) calculated by the random effect model. The results were statistically significant (p=0.01) and moderately heterogeneous (I^2=72%) (Figure 2E). After conducting a sensitivity analysis using an alternative effect model, the findings remained statistically significant [OR=1.31, 95% CI (0.50-0.99), p=0.005] (**Supplementary Figure 3D**). The funnel plot and Egger test (p=0.011) indicated a certain level of publication bias (**Supplementary Figure 1E**). After including five virtual studies, the IOR was 1.752 (p=0.074) (**Supplementary Figure 2C**). Publication bias may have resulted from fewer negative studies being published, which may have affected the results. Overall, hypertension may be a minor risk factor for the development of HCC in NAFLD patients.

Dyslipidemia

After combining the results of 8 studies[14,24,25,27,32-34,36] on the effect of dyslipidemia on the occurrence of HCC in NAFLD patients, the pooled OR was 0.70 (95% CI=0.50-0.99), which was not statistically significant (p=0.05) and demonstrated moderate heterogeneity (I^2=64%) (Figure 2F). The funnel plot and Egger test (p=0.204) revealed no publication bias (**Supplementary Figure 1F**). Consequently, dyslipidemia was not a risk factor, but whether a protective factor needs further investigation.

Older Age

Eight studies[14-16,26,28,32,34,38] were included, and the pooled OR was 3.57, with a 95% CI of (2.74-4.65), and p<0.00001. The heterogeneity was not significant (I^2=28%) (Figure 3A). However, a funnel plot and Egger's test (p=0.018) suggested the possibility of publication bias (**Supplementary Figure 4A**). To address this issue, four virtual studies were included using the Trim and Fill analysis, which yielded an adjusted OR of 6.444 with a p-value of 0.000 (**Supplementary Figure 2D**), indicating that the results were robust.

Male

Male gender was found to be a significant risk factor for HCC in patients with NAFLD. A meta-analysis of eleven studies[20,22,23-25,29,32-34,36,39] showed a pooled OR of 2.45, with a 95% CI of (2.03-2.97), and p<0.00001, with insignificant heterogeneity (I^2=50%) (Figure 3B). The funnel plot and Egger test (p=0.118) suggested no publication bias. Nine studies[14-16,26,30,31,34,38] were reviewed for the impact of gender on patients with NAFLD cirrhosis. The pooled OR was 2.89, with a 95% CI of 2.10-3.98 (p<0.00001). However, there was moderate heterogeneity (I^2=62%) among the studies (Figure 3C), and the funnel plot and Egger test (p=0.001) indicated possible publication bias (**Supplementary Figure 4B-C**). Using the Trim and Fill analysis, three virtual studies were included, yielding an IOR of 3.122 (p=0.000) (**Supplementary Figure 2E**). Additionally, a sensitivity analysis of the included studies was conducted, removing two large

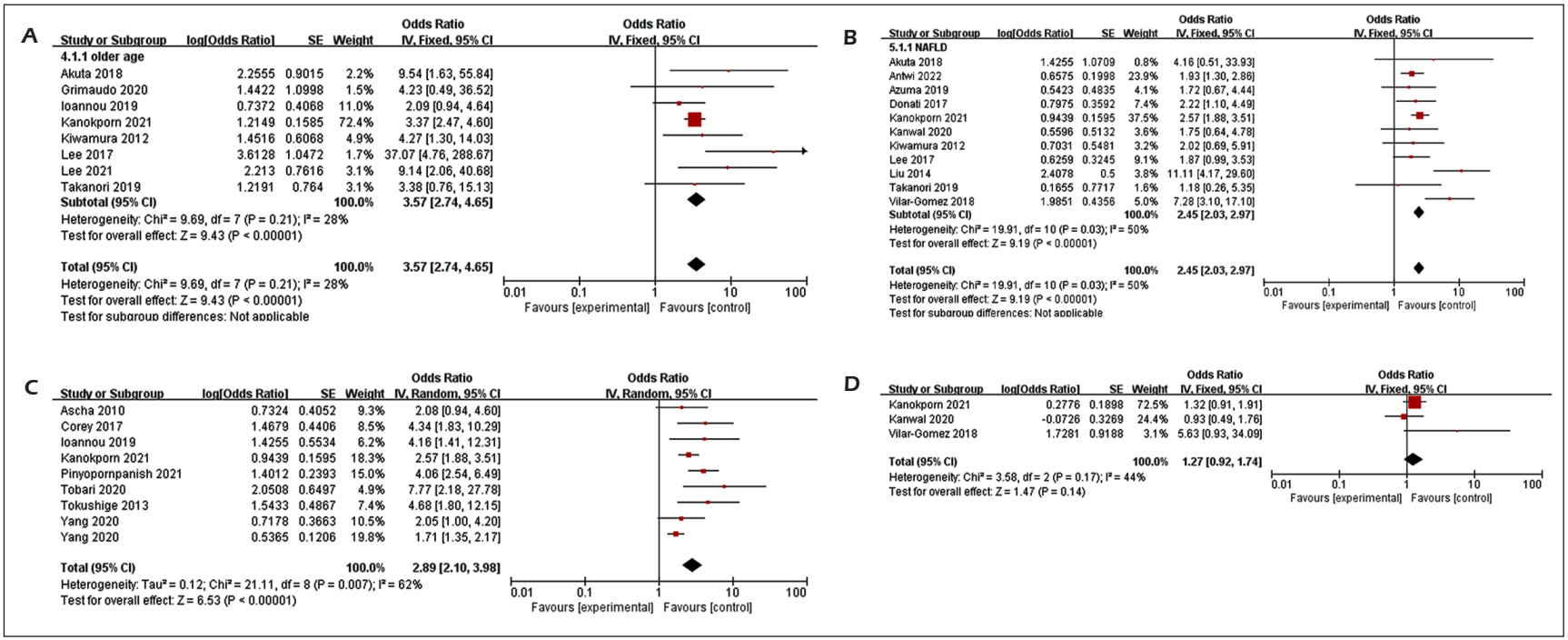

Figure 3. Forest plots depicting (**A**) older age; (**B**) male; (**C**) male in cirrhosis patients; (**D**) Hispanic.

database studies[14,34]. The pooled OR after this exclusion was 3.52 (p<0.00001) (**Supplementary Figure 3E**). Patients with liver cirrhosis who are male may have a higher prevalence of HCC.

Hispanic

3 studies[24,34,39] were included to analyze the impact of Hispanic ethnicity. The pooled result showed an OR=1.27, 95% CI (0.92-1.74) (Figure 3D). Heterogeneity was not significant (I^2=44%), and the Egger test (p=0.481) indicated no publication bias (**Supplementary Figure 4D**). However, the study results did not reach statistical significance (p=0.14). Based on the available evidence, it can be concluded that Hispanic ethnicity may not be a significant risk factor for the development of HCC in NAFLD patients. However, further exploration is needed to confirm this finding.

Alcohol Intake

Four studies[16,22,31,38] were identified that examined the relationship between alcohol intake and the incidence of HCC in patients with NAFLD. The combined result was statistically significant [OR=2.98, 95% CI (1.71-5.18), p=0.044] with acceptable heterogeneity (I^2=43%) (Figure 4A). However, a funnel plot and Egger's test (p=0.044) suggested the possibility of publication bias (**Supplementary Figure 5A**). After including two virtual studies, the IOR was 3.286 (p=0.008) (**Supplementary Figure 2F**). The overall conclusion of the research was consistent with the original findings.

Smoking

Six studies[14,31,34,36,38,39] discussed the impact of smoking on HCC incidence in NAFLD patients. After combining the results, the OR was 1.44, with a 95% CI of (1.24-1.69), and p<0.00001, with a low heterogeneity of 11% (Figure 4B). The absence of publication bias was confirmed through the funnel plot and Egger test (p=0.862) (**Supplementary Figure 5B**). A sensitivity analysis using a different effect model yielded consistent results with the previous analysis [OR=1.44, 95% CI (1.21-1.72), p<0.0001] (**Supplementary Figure 3F**).

PNPLA3 Genotype Variation

4 studies[18,19,28,29] mentioned the influence of *PNPLA3* genotype variation. The pooled OR=1.76 and statistically significant (p=0.0005). The heterogeneity was acceptable (I^2=49%) (Figure 4C). However, the presence of publication bias was indicated by the funnel plot and Egger test (p=0.014) (**Supplementary Figure 5C**). After the inclusion of two virtual studies by the Trim and Fill analysis, the pooled IOR=2.214 (p=0.001) (**Supplementary Figure 2G**). The *PNPLA3* genotype variation may be a less significant risk factor.

Elevated Liver Enzymes

The impact of elevated liver enzymes on the occurrence of HCC in patients with NAFLD was explored in 7 studies[16,20,23,25,32,34,35]. Upon pooling the results, the OR was determined to be 2.92, 95% CI (2.37-3.59) (Figure 5A). The study findings were statistically significant (p<0.0001), and there was no significant heterogeneity (I^2=33%). The funnel plot and Egger test (p=0.257) revealed no indication of publication bias (**Supplementary Figure 6A**). By altering the effect model for sensitivity analysis, the outcome remains unchanged [OR=3.43, 95% CI (2.22-5.32), p<0.00001] (**Supplementary Figure 3G**).

Low Platelet Counts

Low platelet count was found to be an important risk factor for HCC in patients with NAFLD. The pooled OR was 4.61, with a 95% CI of 2.81-7.56, and this result was statistically significant (p<0.0001) without any heterogeneity (I^2=0%) (Figure 5B). However, there was evidence of publication bias as indicated by the funnel plot and Egger test (p=0.029) (**Supplementary Figure 6B**). Using the Trim and Fill analysis, three virtual studies were included, and the pooled OR was 13.124 (p=0.000) (**Supplementary Figure 2H**). The results are relatively robust.

Low Albumin Levels

The presence of low albumin levels in NAFLD patients increased the risk of developing HCC [OR=2.11, 95% CI (1.11-4.00), p=0.02]. There was no heterogeneity between studies (I^2=0%) (Figure 5C). The absence of publication bias was confirmed by the funnel plot and Egger test (p=0.183) (**Supplementary Figure 6C**). Sensitivity analysis using a random effect model produced consistent results [OR=2.11, 95% CI (1.11-4.00), p=0.02] (**Supplementary Figure 3H**).

High Ferritin

3 studies[17,25,32] explored the relationship between high ferritin and the incidence of HCC in NAFLD patients. The pooled OR was 1.31, with a 95% CI of 0.79-2.16. However, the result was

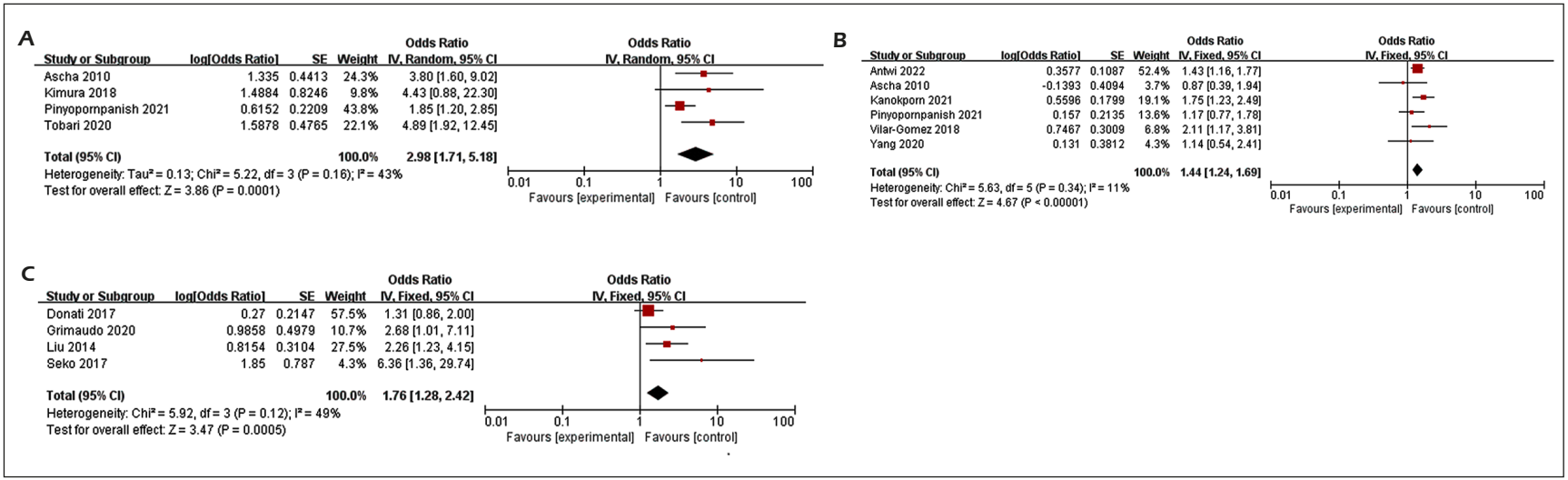

Figure 4. Forest plots depicting (**A**) alcohol intake; (**B**) smoking; (**C**) *PNPLA3* genotype variation.

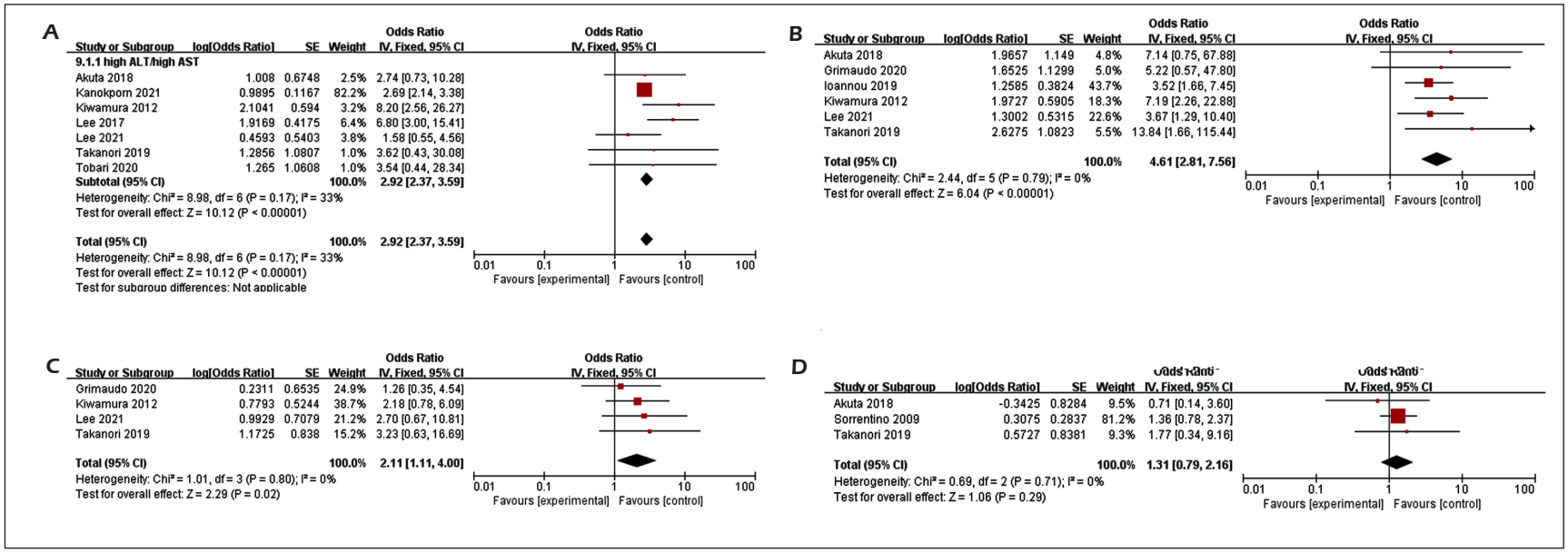

Figure 5. Forest plots depicting (**A**) elevated liver enzymes; (**B**) low platelet count; (**C**) low albumin (**D**) high ferritin.

not statistically significant (p=0.29), and there was no heterogeneity (I^2=0%) (Figure 5D). The funnel plot and Egger test both provided evidence that there is no publication bias (p=0.849) **(Supplementary Figure 6D)**. These results suggested that high ferritin may not be a significant risk factor.

Discussion

Given the increasing prevalence of NAFLD and the lack of viable therapeutic alternatives, there is a high likelihood of NAFLD advancing. Despite the increased focus on NAFLD-associated HCC, there is a lack of comprehensive and conclusive data regarding its predisposing factors. Our study conducted a systematic review and meta-analysis to comprehensively identify the main risk factors associated with the development of HCC in patients with NAFLD.

The study highlighted advanced fibrosis as the most potent risk factor for the development of HCC in patients with NAFLD, with an OR of 6.40. The liver's persistent chronic injury triggers a cascade of events, including hepatocyte apoptosis, inflammation, activation of hepatic stellate cells, and the production of myofibroblasts in the extracellular matrix. This leads to compensatory hepatocyte proliferation and the release of reactive oxygen species, ultimately resulting in DNA damage. This continuous cycle of destruction-regeneration is believed to cause replication-related mutations in hepatocytes, ultimately leading to the development of HCC[43,44].

Metabolic diseases such as diabetes, obesity, and hypertension are risk factors for NAFLD-related HCC, while dyslipidemia is not. Diabetes is strongly associated with HCC, while obesity and hypertension are weakly associated with HCC. Aberrant metabolism is a prevalent complication of NAFLD and exhibits a direct correlation with the extent of NAFLD damage[45]. Diabetes may promote the occurrence of liver cancer by activating the inflammatory cascade, producing pro-inflammatory factors and reactive oxygen species, leading to genomic instability, cell proliferation and inhibiting hepatocyte apoptosis[46,47]. The use of hypoglycemic agents, such as metformin, may improve disease progression in HCC[48]. Obesity is related to chronic inflammation and lipid metabolism disorders, which can form a carcinogenic state and promote the occurrence of liver cancer[49,50]. Multiple risk factors are more correlated with each other, and the possible synergistic effect of obesity and hypertension on HCC cannot be ruled out[51]. Demographic indicators such as older age and male are risk factors for HCC development in NAFLD, and whether Hispanic is a risk factor needs to be further studied. Older age may lead to genomic instability, somatic mutations, changes in gene expression, and DNA methylation, which may affect the development of HCC[52]. Males are risk factors for HCC in NAFLD, and the association with HCC is stronger in patients with NAFLD cirrhosis. Previous genetic studies[53,54] have pointed to androgens and androgen receptors as part of the reason for sex differences in chronic liver disease and liver cancer. Estrogen and androgens are steroid hormones that mediate their effects by binding to nuclear receptors and regulating gene expression as transcription factors. The inhibition of the estrogen receptor and the increase of androgen receptor expression may be related to the development of HCC[54]. Being Hispanic was found to be an associated risk factor (OR=1.27), but it was not statistically significant. While we believe this risk factor is of concern, the evidence is insufficient to draw a definitive conclusion.

Alcohol intake and smoking are both risk factors for the development of HCC in NAFLD patients. Alcohol intake is strongly associated with HCC (OR=2.98). The mechanisms by which alcohol promotes HCC include malnutrition caused by long-term alcohol intake, hepatic stellate cell activation, fibrosis promotion effect of alcohol and its metabolites, oxidative stress of liver tissue, and immune response[55]. Studies[56] have demonstrated a significantly increased incidence of HCC in the smoking population through meta-analysis. Tobacco contains a variety of carcinogens, such as nitrosamines, hydrocarbons, tar, etc. While the liver is the main metabolic and detoxification organ of these products, long-term exposure to these carcinogens may induce malignant tumors[57].

The result of this study showed that *PNPLA3* genotype variation (encoding I148M variation) was associated with an increased risk of HCC in NAFLD. The *PNPLA3* gene encodes a protein associated with triglyceride lipase, which is involved in lipid regulation[58]. The findings of a meta-analysis indicate that the *PNPLA3* genotype G allele could potentially be correlated with the severity of NAFLD[59]. Attention to genetic problems may lead to new ways to prevent them.

Abnormal hematological indicators, such as elevated liver enzymes, low platelet count, and low albumin, are risk factors for the development of HCC in NAFLD patients. High ferritin levels are a risk factor of concern but require further study as they were not statistically significant. Abnormal liver transaminase levels may not be present in NAFLD, but liver transaminase is a reference index to reflect liver function impairment and evaluate the degree of liver inflammation, necrosis, and fibrosis[60]. Platelet count is an ideal biomarker to measure the severity of liver fibrosis. Low platelet count reflects impaired liver function and a serious degree of fibrosis[61]. Similarly, albumin is made by the liver, and low serum albumin levels reflect impaired liver synthesis[62]. However, the number of included studies in our analysis is small, and further research is needed to confirm these findings.

Limitations

It is important to note that the pooled data on hypertension, older age, alcohol intake, low platelet count, and *PNPLA3* genotype variation may have some publication bias, as negative studies may have been underrepresented. Additionally, the risk factors adjusted may not be identical across studies, which can affect the accuracy of the results. Therefore, further research is needed to confirm the findings and address these limitations. It is worth noting that although we extracted adjusted OR values whenever possible, few studies adjusted for all possible confounding factors, which may lead to heterogeneity in the studies. Additionally, the NAFLD patients involved in some studies may have severe lesions and may not represent the population with mild lesions or the general population. However, these studies are still of profound reference value and provide important insights into the risk factors associated with HCC development in NAFLD patients. Further research is needed to confirm these findings and address any limitations.

Conclusions

Our study systematically and comprehensively analyzed the current possible risk factors and made a comprehensive assessment. Based on the results of this study, Advanced liver fibrosis, diabetes, obesity, hypertension, older age, male, alcohol intake, smoking, *PNPLA3* genotype variation, elevated liver enzymes, low platelet counts, and low albumin levels were all risk factors for HCC in NAFLD. Hispanic and high ferritin levels were possible risk factors that need further exploration. Dyslipidemia was not a risk factor. We should strengthen prevention for individuals without risk factors. Individuals with existing risk factors should be monitored, and the progression of NAFLD to HCC should be prevented through clinical intervention. Further prospective clinical studies and mechanism studies on NAFLD-related HCC risk factors are needed to provide better ideas for clinical diagnosis and treatment.

Conflict of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Ethics Approval and Informed Consent

Not applicable.

Availability of Data and Materials

All data were sourced from published studies and are accessible to anyone interested.

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Authors' Contribution

GW conceived and designed the study. GW and ZH performed the studies search and analyzed the data. GW wrote the manuscript. LL edited the article and provided the necessary guidance. The article's submission and publishing were approved by all authors.

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