Risk Factors of Hepatocellular Carcinoma in Non-alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis

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Abstract

To better identify people at high risk of developing hepatocellular carcinoma (HCC) in non-alcoholic fatty liver disease (NAFLD), we aimed to conduct a systematic review and meta-analysis. Databases (including MEDLINE, EMBASE, Web of Science, the Cochrane Library, ClinicalTrials.gov) were searched up to March 2021. We included studies that reported odds ratios (ORs) or hazard ratios (HRs) and 95% confidence intervals. 24 studies (3 prospective cohort studies, 16 retrospective cohort studies, and 5 case-control studies) of 23 articles, with a total of 1004284 NAFLD cases and 3610 NAFLD-HCC cases, were finally included. The pooled data suggested male, older age, diabetes, low platelet count, and advanced liver fibrosis were important risk factors for HCC in NAFLD. Hypertension, overweight, low albumin, PNPLA3 genotype, dyslipidemia, abnormal liver enzymes were also risk factors worth concern. This study may contribute to the establishment of targeted screening and secondary prevention of HCC in patients with NAFLD.

Introduction

The spectrum of NAFLD is broad, including non-alcoholic simple fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), related cirrhosis and hepatocellular carcinoma (HCC). It is estimated that one-quarter of the global population suffers from non-alcoholic fatty liver disease (NAFLD)[1]. The incidence of NAFLD is projected to increase by up to 56% in the next ten years[2,3]. HCC is the most common type of primary liver cancer. The leading reasons for HCC were usually hepatitis viruses or alcohol in the past [4]. In recent years, in parallel with the prevalence of obesity and insulin resistance, NAFLD-related HCC has gradually become not negligible[5-7].

The incidence of HCC in patients with NAFLD is estimated to be 0.44/1000 person-years and 9-26/1000 person-years in patients with NASH cirrhosis[5,8-10]. Misdiagnosis and the tendency to label NAFLD-related cirrhosis as "cryptogenic cirrhosis" has delayed people's awareness of the increased risk of HCC in NAFLD [11]. Current treatment options for hepatocellular carcinoma are very limited[12]. The evidence shows that the NAFLD-related HCC has a more insidious course, with larger tumors and a worse prognosis[13-16].

It is necessary to take urgent measures to raise global awareness and identify the high-risk subgroups of HCC among patients with NAFLD. However, to our knowledge, no quantitative review has been published to explore the risk factors. Therefore, we conducted a systematic review and meta-analysis to synthesize evidence, and systematically review the risk factors that may predict the occurrence of HCC in NAFLD risk populations.

Methods

Search strategy and selection criteria

Potentially relevant studies were identified through systematic searches of relevant databases (including MEDLINE, EMBASE, Web of Science, the Cochrane Library, Clinical Trials.gov) in January 2021. No date or language restrictions were applied. Reference lists from potentially relevant papers and previous review articles were hand-searched. Medical Subject Headings and free text terms for non-alcoholic fatty liver disease, risk factors, and hepatocellular carcinoma were used. The search strategies of MEDLINE, EMBASE, Web of Science were available in **Suppl.Table.1**. Searches were updated in March 2021.

We combined and deduplicated search results from the 5 databases before screening for eligibility. NAFLD included unspecified NAFLD, NASH, NAFLD cirrhosis. NAFLD and HCC could be diagnosed by clinical, imaging, or liver biopsy. All studies were cohort studies or case-control studies which could provide odds ratios (ORs) or hazard ratios (HRs) and 95% confidence interval, or the values could be completed by calculation. All included literature was of high quality. We excluded case reports, reviews, guidelines, animal experiments, etc. The research with incomplete data or unavailable full text were also excluded.

We conducted a meta-analysis of a risk factor only if more than 2 studies examined it, otherwise, we only conducted a systematic review of the risk factor. All studies were carefully reviewed by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[50] (**Suppl.Table.2**)

Data extraction and literature quality assessment

The search results were screened independently by two researchers strictly according to the above-mentioned established criteria. They discussed with each other or viewed the full text for processing when they met disagreement. Information was finally extracted from the studies, including author, publication year, country, the number of patients diagnosed with NAFLD, number of HCC cases, adjustments, effect value.

Two authors independently assessed the risk of bias by using the Newcastle-Ottawa Scale (NOS), judging studies based on points awarded for selection of study groups, comparability of groups and exposure/outcome ascertainment. Studies with scores ≥6 points were considered to be of high quality.

Data synthesis and analysis

We carried out meta-analyses in RevMan5.3 software and calculated pooled summary effect estimates using the inverse-variance weighting of ORs / HRs. Quantified between-study heterogeneity using the I^2 statistic; the significance of heterogeneity was investigated using Cochran's Q test (p threshold = 0.05). When $I^2 \leq 50\%$, we took a fixed-effect model for analysis; When $I^2 > 50\%$, we took a random-effect model. Egger test was used to analyze publication bias in Stata 15.1 software. If $P>0.05$, it indicated that there was no obvious publication bias. In addition, sensitivity analysis was performed by comparing the difference between the point estimate and the interval estimate of the combined value in different effect models.

Results

Study selection and study characteristics:

A total of 10472 articles were obtained by preliminary search. After screening the titles and abstracts, 546 articles were selected for full-text screening, of which 523 articles were excluded due to the reasons reported in the PRISMA chart **(Figure 1)**. In the end, this study included 24 studies (3 prospective cohort studies, 16 retrospective cohort studies, and 5 case-control studies) of 23 articles. Perform NOS scores on these articles. The basic characteristics of included literature could be seen in **Table 1**. The research includes studies from Asia (Japan [13,17,18,19,20,23,24,26,28,29,32,33] and China [22], South Korea[25]), Europe (UK[21], Italy[30,31,36]), and North America (United States[10,27,34,35,37]) with 1004284 NAFLD cases and 3610 HCC cases.

Table 1. Baseline characteristics of all the studies included in the meta-analysis.

Study	Country	Study design	Number of patients diagnosed with NAFLD	Number of HCC cases	Adjustments	Effect value	NOS scores
Tokushige 2013[17]	Japan	case-control	574(histological)	41	age、gender、fibrosis、other metabolic RFs	OR	7
Tobari 2019[18]	Japan	prospective cohort	××××Imaging or histological×	119	age、gender、alcohol、cirrhosis、other metabolic RFs	OR	9
Seko 2015[19]	Japan	retrospective cohort	312 ×histological×	6	age、gender、fibrosis、other metabolic RFs	HR	9
Seko 2017[20]	Japan	retrospective cohort	××××histological×	10	age、gender、PNPLA3、fibrosis、other metabolic RFs	HR	9
Liu 2014[21]	UK	case-control	××××histological or others×	100	age、gender、PNPLA3、fibrosis/ cirrhosis、other metabolic RFs	OR	7
Lee 2017[22]	China	retrospective cohort	××××××coding×	494	age、gender、ALT、BP、TC、DM、statin、metformin、aspirin	HR	9
Kogiso 2020[23]	Japan	retrospective cohort	××××histological×	26	age、gender、fibrosis、other metabolic RFs	HR	8
Kimura 2018[24]	Japan	retrospective cohort	××××histological×	×	age、gender、fibrosis、other metabolic RFs	OR	8
Kim 2017[25]	Korea	retrospective cohort	×××××ultrasound×	23	age、gender、fibrosis、other metabolic RFs	HR	8
Kawamura 2012[26]	Japan	retrospective cohort	×××××ultrasound×	××	age、gender、other metabolic RFs	HR	8
Kanwal 2018[13]	US	retrospective cohort	××××××coding×	×××	age、race、other metabolic RFs	HR	8
Kanwal 2020[27]	US	retrospective cohort	××××××coding×	×××	age、gender、race、DM、BP、	HR	9

					dyslipidemia BMI		
Ito 2019[28]	Japan	retrospective cohort	ultrasound or clinical		age gender other metabolic RFs	HR	6
Hashimoto 2009[29]	Japan	prospective cohort	histological		age fibrosis other metabolic RFs	OR	8
Grimaudo 2020[30]	Italy	prospective cohort	histological or clinical		gender age PNPLA3 fibrosis other metabolic RFs	HR	9
Donati 2017[31]	Italy	retrospective cohort			age gender BMI DM fibrosis PNPLA	OR	8
Akuta 2018[32]	Japan	retrospective cohort	histological		age gender fibrosis other metabolic RFs	HR	7
Azuma 2019[33]	Japan	case-control	histological or imaging		age gender fibrosis other metabolic RFs	OR	9
Ioannou 2019[34]	US	retrospective cohort	coding	1278	age gender DM BMI PLT ALB AST/ALT	HR	9
Yang 2020[35]	US	retrospective cohort studies	coding coding		age gender race other metabolic RFs	HR	9
Sorrentino2009[36]	Italy	case-control	482 histological	71	age gender other metabolic RFs	HR	7
Corey 2017[37]	US	case-control	histological or clinical	94	age gender other metabolic RFs	OR	9
Ascha 2010[10]	US	retrospective cohort	histological or imaging		age gender smoking alcohol BMI DM	HR	9

Abbreviations: CI, confidence interval; HR, risk ratio; OR ratio; NAFLD, non-alcoholic fatty liver disease; RF, risk factors; DM, diabetes; AFP, metformin; ALT, glutamate transaminase; AST, aspartate Transaminase PNPLA3: PNPLA3 genotypes metabolic

RFs include: BMI, DM, BP, lipids, blood tests (total bilirubin, ALB, AST, ALT, ALP, γ-GTP, PLT, clotting enzyme duration)

Risk factors and HCC in NAFLD

All pooled data were shown in **Figure 2**. By combining the HRs of univariate analysis, the statistically significant factors were: male, low platelet count, advanced liver fibrosis, diabetes, hypertension (see **Figure 2a**). There were 4 factors statistically significant by combining the ORs of multivariate analysis: male, older age, diabetes, advanced liver fibrosis (see **Figure 2b**). 4 factors were statistically significant by combining the HRs of multivariate analysis: male, low platelet count, diabetes, advanced liver fibrosis (see **Figure 2c**). The results of publish bias assessment were shown in **Suppl. Table 3**.

Male A total of 14 observational studies suggested that the risk of HCC in NAFLD was associated with gender. 6 of the studies conducted a univariate analysis to obtain HRs [pooled HR=1.63, 95%CI (1.33-2.01), P<0.00001] (**Figure 2, Figure 3a**), with 5 studies conducting multivariate analysis to obtain HRs [pooled HR=1.79, 95%CI (1.46-1.21), P<0.00001] (**Figure 2, Figure 5a**). 5 studies conducted multivariate analysis to obtain ORs [pooled OR=4.38, 95%CI (2.93-6.57), P<0.00001] (**Figure 2, Figure 4a**). According to Egger test results (**Suppl. Table 3**) and forest plots, the combined values had good homogeneity, and there was a certain publication bias in pooled multivariate analysis OR values but there was no obvious publication bias in both pooled univariate and multivariate analysis HRs. Thus, we concluded that the gender factor male was an important risk factor for the development of NAFLD to HCC.

Diabetes Diabetes was diagnosed by any of the following criteria: (i) classic symptoms of hyperglycemia and random plasma glucose≥200 mg/dl; (ii) fasting plasma glucose≥126 mg/dl; (iii) 2-h post-glucose (oral glucose tolerance test)≥200 mg/dl; (iv) HgbA1C≥6.5%[38]. 13 studies mentioned this factor. The type of diabetes included in 4 of the studies was type 2 diabetes[30,31,32,34] and the others were unspecified diabetes. There were 6 studies conducting univariate analysis to obtain HR values [pooled HR=2.58, 95%CI (1.40-4.75), P<0.00001] (**Figure 2, Figure 3b**). 7 studies conducted multivariate analysis to obtain HRs [pooled HR=1.64, 95%CI (1.13-2.36), P=0.008] (**Figure 2, Figure 5b**) and 4 studies conducted multivariate analysis to obtain ORs [pooled OR=3.65, 95%CI (2.32-5.75), P<0.00001] (**Figure 2, Figure 4b**). According to Egger test results, there was no significant publication bias (**Suppl. Table 3**). The results suggested that NAFLD patients with diabetes had a higher risk to suffer from HCC.

Advanced liver fibrosis There were 10 studies that mentioned advanced liver fibrosis as a risk factor. When the included participants underwent liver biopsy, the NAFLD pathological stage was evaluated according to the classification of Brunt et al[39]. Fibrosis ≥F3 was defined as advanced fibrosis[20,21,23,24,28,29,31,32]. Otherwise, the severity of liver fibrosis was assessed by two noninvasive markers, NAFLD fibrosis score and fibrosis-4 score[16,33]. 3 studies conducted the univariate analysis to obtain HRs [pooled HR=21.32, 95%CI (8.74-52.02), P<0.00001] (**Figure 2, Figure 3c**). 4 studies conducted multivariate analysis to obtain HR values [pooled HR=11.98, 95%CI (4.93-29.12), P<0.00001] (**Figure 2, Figure 5c**). And 6 studies conducted multivariate analysis to obtain OR values [pooled OR=5.15, 95%CI (2.66-9.95), P<0.00001] (**Figure 2, Figure 4c**). There was no obvious publication bias in both pooled multivariate analysis HRs and ORs (**Suppl. Table 3**). Thus, we concluded that advanced fibrosis was a significant predictor of HCC in NAFLD, which could substantially increase the risk of HCC.

Older age A total of 11 observational studies involved in the factor, older age. The results of the pooled univariate analysis HRs were not statistically significant (**Figure 2**). Pooled multivariate analysis of HRs and ORs results showed that factor older age could increase the risk of HCC in NAFLD by 1.16-fold and 3.62-fold, respectively (**Figure 2, Figure 4d, Figure 5d**). Results were publication-biased and heterogeneous. The high heterogeneity might be due to different research "abnormal" cut-off points. According to a large retrospective study by Lee et al, which included 18080 NAFLD patients, the 10-year cumulative incidences of HCC were shown to be increasing along with age levels: 18-45 years (0.19%; 95% CI, 0-0.57), 46-55 years (1.31%; 95%, CI, 0-2.86), 56-65 years (3.80%; 95% CI, 1.02-6.59), and >65 years (6.20%; 95% CI, 3.20-9.20) [22]. Despite the large heterogeneity between studies, we still considered older age to be an important predictor of HCC.

Low platelet count There were 5 studies included in total. 3 of the studies set the threshold for platelet count at 150×10^9/L [27,29,37], 1 at 200×10^9/L[33] and 1 at 190×10^9/L [31]. The results of pooled univariate analysis of HRs showed that low platelet count increased HCC risk 13.53-fold [HR=13.53, 95%CI (6.35-28.84), P<0.00001] (**Figure 2, Figure 3d**). The results

of pooled multivariate analysis of HRs showed that low platelet count increased HCC risk 7.39-fold [HR=7.39, 95%CI (3.47-15.74), P<0.00001] (**Figure 2, Figure 5e**). The results showed good homogeneity and no publication bias (**Figure 5e, Suppl. Table 3**).

Hypertension 9 studies did research in the factor hypertension. The results of pooled multivariate analysis of HRs were not statistically significant (**Figure 2**). Pooled univariate analysis of HRs results showed that factor hypertension could increases the risk of HCC in NAFLD by 3.14-fold [HR=3.14, 95%CI (1.32-7.50), P=0.01] with no obvious publication bias (**Figure 3e, Suppl. Table 3**).

Sensitivity analysis

We limited the analysis to studies judged to be at low risk of bias and conducted sensitivity analysis by comparing the difference between the point estimate and the interval estimate of the combined effect size, when different effect models were compared. The results showed that the combined effect size conclusions of all factors had no significant change, indicating that the meta-analysis results of various indicators in this study were stable. The high levels of heterogeneity between studies for some factors, as indicated by the high I^2 values, were explored. These were felt to be due to the variation in study design, particularly around the range of populations and outcomes studied, leading to clinical heterogeneity. Our research pooled univariate analysis HRs, multivariate analysis ORs and HRs. There was a consistent direction of effect. Based on the objective of the review, pooling using meta-analysis was still felt to be appropriate.

Other risk factors

Other factors, such as low albumin, patatin-like phospholipase domain containing 3 (PNPLA3) genotype, abnormal liver enzymes, overweight, and dyslipidemia had also been reported as possible risk factors, but there were too few reports to be pooled or the pooled results not statistically significant.We conducted a systematic review of the risk factors.

low albumin A total of 5 studies mentioned low albumin levels as a risk factor [26,28,29,30,35]. The studies by Kawamura et al[26] and Grimaudo et al[30] conducted univariate analysis, and the results showed that low albumin levels can increase HCC risk by 2.18-fold and 1.26-fold respectively, but both were not statistically significant. The research of Yang et al[35] included 2 cohort studies. One included 354 patients with NASH cirrhosis over 10 years of follow-up at the Mayo Clinic, and the other included 6630 patients who enrolled on the liver transplantation waiting list due to NAFLD. The results of the 2 cohort studies both showed that low albumin levels increased the risk for NAFLD developing HCC [HR=0.48, 95% CI (0.36-0.68), P<0.001] [HR=0.67, 95% CI (0.54-0.82), P<0.001].

PNPLA3 genotype The role of the PNPLA3 genotype was well recognized as a modifier of hepatic triacylglycerol accumulation and NAFLD progression[40]. A total of 4 articles suggested that the PNPLA3 genotype was a risk factor for HCC in NAFLD, especially the GG genotype. The multivariate analysis results of Grimaudo et al[30] and Danti et al[31] suggested that the PNPLA3 genotype increased the risk of HCC in patients with NAFLD by 168% and 61% respectively. Seko et al. showed a 6.36-fold increased risk for the PNPLA3 genotype GG [HR=6.36, 95%CI (1.36-29.8), P=0.019][20]. The research by Liu et al[21] which include 2 single-center studies, concluded that that carrying each G allele was associated with a doubled risk of HCC [OR=2.26, 95%CI (1.23-4.14), P=0.0082].

Dyslipidemia 7 studies investigated lipid levels and their prognostic value for HCC[22,23,24,26,27,28,32]. Low high-density lipoprotein, high triglycerides, combined lipid abnormalities, and hypercholesterolemia were exposures of interest. Our meta-analysis showed the results no significance (**Figure 2**). The relationship between dyslipidemia and HCC progression needed to be further investigated. It has been suggested that dyslipidemia is associated with NAFLD progression and that statins may have a protective effect on HCC progression [HR=0.29, 95% CI (0.12-0.68), P=0.005] [22]. Dyslipidemia remained a risk factor of concern.

Overweight 5 studies reported overweight and HCC. All studies used body mass index (BMI) to measure overweight. Some studies analyzed the effect of BMI>25 on the development of HCC in NAFLD, with the other analyzed BMI>30. Being overweight was an independent risk factor of HCC. But our meta-analysis results seem to be negative and not statistically significant (**Figure 2**). The relationship between overweight and HCC in NAFLD needs to be further explored.

Abnormal liver enzymes 6 studies investigated the predictive value of liver function abnormalities, studying high AST, high ALT, or high ALT/AST. High AST was mentioned as a risk factor in 4 studies [23,26,28,30]. A large retrospective study in Japan suggested an 8-fold increase in HCC risk with AST≥40IU[26]. 4 studies mentioned high ALT as a risk factor[17,22,26,28]. Lee's large study suggested a 6-fold increase in risk with high ALT[22]. One study mentioned AST/ALT>12.83 increased nearly 5-fold in HCC risk[34]. We should pay attention to liver enzyme abnormalities in patients with NAFLD, which may be associated with the development of HCC.

Discussion

NAFLD-related HCC is an end-type liver disease of NAFLD, the pathogenesis of which is still unclear[1]. It is important to explore the risk factors associated with the development of HCC in NAFLD to provide a basis for targeted screening in patients with NAFLD. In this systematic review and meta-analysis, male, older age, diabetes, low platelet count, and advanced liver fibrosis were confirmed to be important risk factors for HCC in NAFLD. Hypertension, overweight, low albumin, PNPLA3 genotype, dyslipidemia, abnormal liver enzymes were also risk factors worth concern.

In our study, we found the gender male increases the 1.63-4.38 folds risk of HCC in NAFLD by pooled results. Previous genetic studies showed that androgens and androgen receptors (Ars) are part of the cause of the gender differences in liver disease and liver cancer. Both estrogen and androgen are steroid hormones that mediate their action by binding to nuclear receptors and acting as transcription factors to regulate the expression of multiple genes. Progression from hyperplasia to HCC may be associated with suppression of estrogen receptors and elevated AR expression[41,42].

Metabolic-related factors were considered as risk factors. Diabetes itself is associated with the development of liver cancer[43]. Diabetes promotes hepatocarcinogenesis via activation of inflammatory cascades with the production of proinflammatory cytokines and reactive oxygen species, which cause genomic instability, promote cellular proliferation, and inhibit apoptosis of hepatocytes[44]. In the future, more extensive studies could explore whether the impact of diabetes on the risk of NAFLD-related HCC can change by using antidiabetic drugs and the effectiveness of diabetes control. Other metabolic factors like overweight also play a role in disease progression. Existing research pointed out that obesity and insulin resistance can lead to chronic inflammation, changes in lipid metabolism, and a carcinogenic state that promotes the development of liver cancer[45]. But our meta-analysis results seem to be negative and not statistically significant. We carefully reviewed the studies included. Most of the statistical results in our included studies for overweight or obesity were not statistically significant, either in univariate or multivariate analysis. It may be due to the presence of other confounding factors. Previous studies have shown that hypertension was related to severe liver disease outcomes[46]. In this study, hypertension was also confirmed as a risk factor related to the occurrence of HCC in NAFLD patients. Since there were few studies included (4 articles) that might indicate insufficient evidence, more research should be taken to explore it.

In addition, we should direct our gaze to advanced liver fibrosis. In a multi-center Japanese cohort comprising 596 patients with NAFLD-related HCC diagnosed between 1991 and 2010, 36.6% did not have cirrhosis[47]. Consistent with these findings, in a multi-center Italian cohort comprising 145 patients with NAFLD-related HCC enrolled between 2010 and 2012, 50% did not have cirrhosis[48]. The stage of fibrosis might be relevant in the future risk of HCC in the absence of cirrhosis[1]. The higher estimates were found in cohorts with a higher degree of NASH or stage of fibrosis[49]. Platelet count was an ideal biomarker of the severity of fibrosis. Our study confirmed that, low platelet count could also predict NAFLD to develop HCC, which was considered related to its ability to predict the severity of liver fibrosis.

The limitation of this study was that, many studies were based on liver biopsy, which mainly came from cohort studies in clinics and hospitals or transplant registration databases. Those may have inherent selection bias (Not representative of the general NAFLD population) and relatively short median follow-up time. However, these studies provide essential comparisons and supporting evidence. Based on the objective of the review, it was still appropriate to conduct meta-analyses.

In summary, based on our results, for the general NAFLD population, we can focus on these risk factors to prevent adverse liver outcomes. For patients with NASH or NASH cirrhosis, the risk factors we identified might serve as essential targets for secondary prevention to modify the progression of NAFLD to HCC. Further prospective clinical studies are still needed to explore the risk factors in NAFLD-related HCC, which will provide better ideas for clinical diagnosis and treatment.

Declarations

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Author Contributions

Dr. Wenpei Guo performed the study and wrote the paper. Dr. Lixin Liu designed the study and reviewed the manuscript. They worked together to assess the articles enrolled in this study and collected the data.

Additional Information

Supporting information

Suppl. Table 1 Search strategy

Suppl. Table 2 Checklist

Suppl. Table 3 Bias assessment

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

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Figures

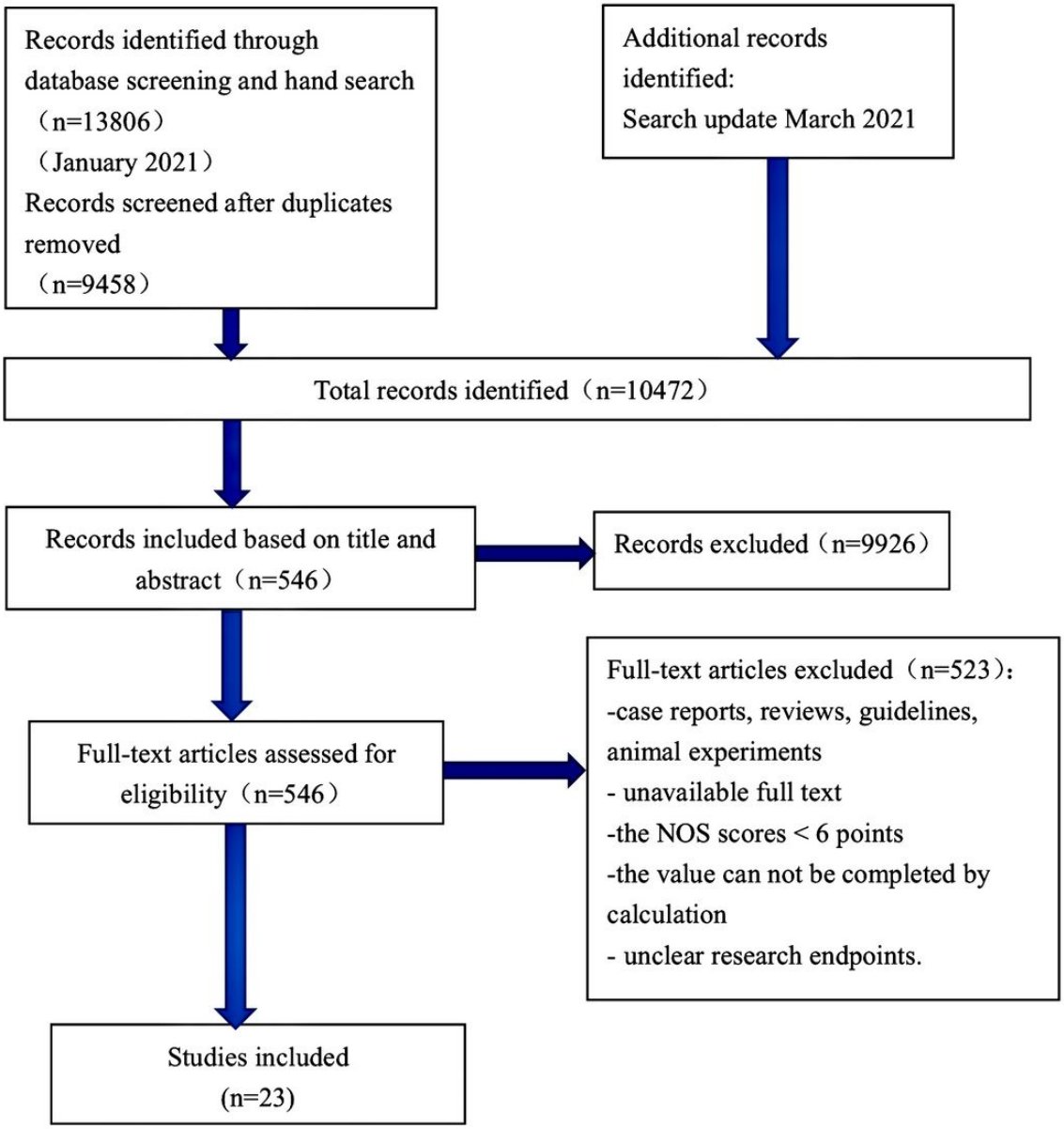

Figure 1. PRISMA diagram of study selection.

Figure 1

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a

Risk factors	Number of studies	Heterogeneity test		Effects model	HRs	95%CI	P value of Z test
		I^2 (%)	P value				
male	6	0%	0.46	fixed	1.63	1.33-2.01	<0.00001
older age	5	84%	<0.0001	random	1.11	0.99-1.25	0.07
diabetes	6	85%	<0.00001	random	2.58	1.40-4.75	<0.00001
overweight	5	39%	0. 16	fixed	1.00	0.96-1.04	0.89
low platelet count	3	0%	0.59	fixed	13. 53	6.35-28.84	<0.00001
hypertension	4	67%	0.03	random	3.14	1.32-7.50	0.01
dyslipidemia	4	70%	0.02	random	0.82	0.34-1.96	0.65
advanced fibrosis	3	0%	0.71	fixed	21.32	8.74-52.02	<0.00001

b

Risk factors	Number of studies	Number of studies		Effects model	ORs	95%CI	P value of Z test
		I^2 (%)	P value				
male	5	49%	0.10	fixed	4.38	2.93-6.57	<0.00001
older age	5	79%	0. 0007	random	1.16	1.09-1.24	<0.00001
diabetes	4	2%	0.38	fixed	3.65	2.32-5.75	<0.00001
overweight	4	67%	0. 03	random	0.96	0.91-1.00	0.08
advanced fibrosis	6	77%	0.0006	random	5.15	2.66-9.95	0.00001

c

Risk factors	Number of studies	Number of studies		Effects model	HRs	95%CI	P value of Z test
		I^2 (%)	P value				
male	5	37%	0.17	fixed	1.79	1.46-1.21	<0.00001
older age	6	63%	0.02	random	3.62	1.79-7.33	<0.00001
diabetes	7	77%	0.0003	random	1.64	1.13-2.36	0.008
low platelet count	4	0%	0.98	fixed	7.39	3.47-15.74	<0.00001
hypertension	4	46%	0.14	fixed	1.17	0.93-1.49	0.19
dyslipidemia	3	55%	0.11	random	1.00	0.71-1.41	0.02
advanced fibrosis	4	0%	0.88	fixed	11.98	4.93-29.12	<0.00001

Figure 2. (a) The results of pooled univariate analysis HRs. **(b)** The results of pooled multivariate analysis ORs. **(c)** The results of pooled multivariate analysis HRs.

Figure 2

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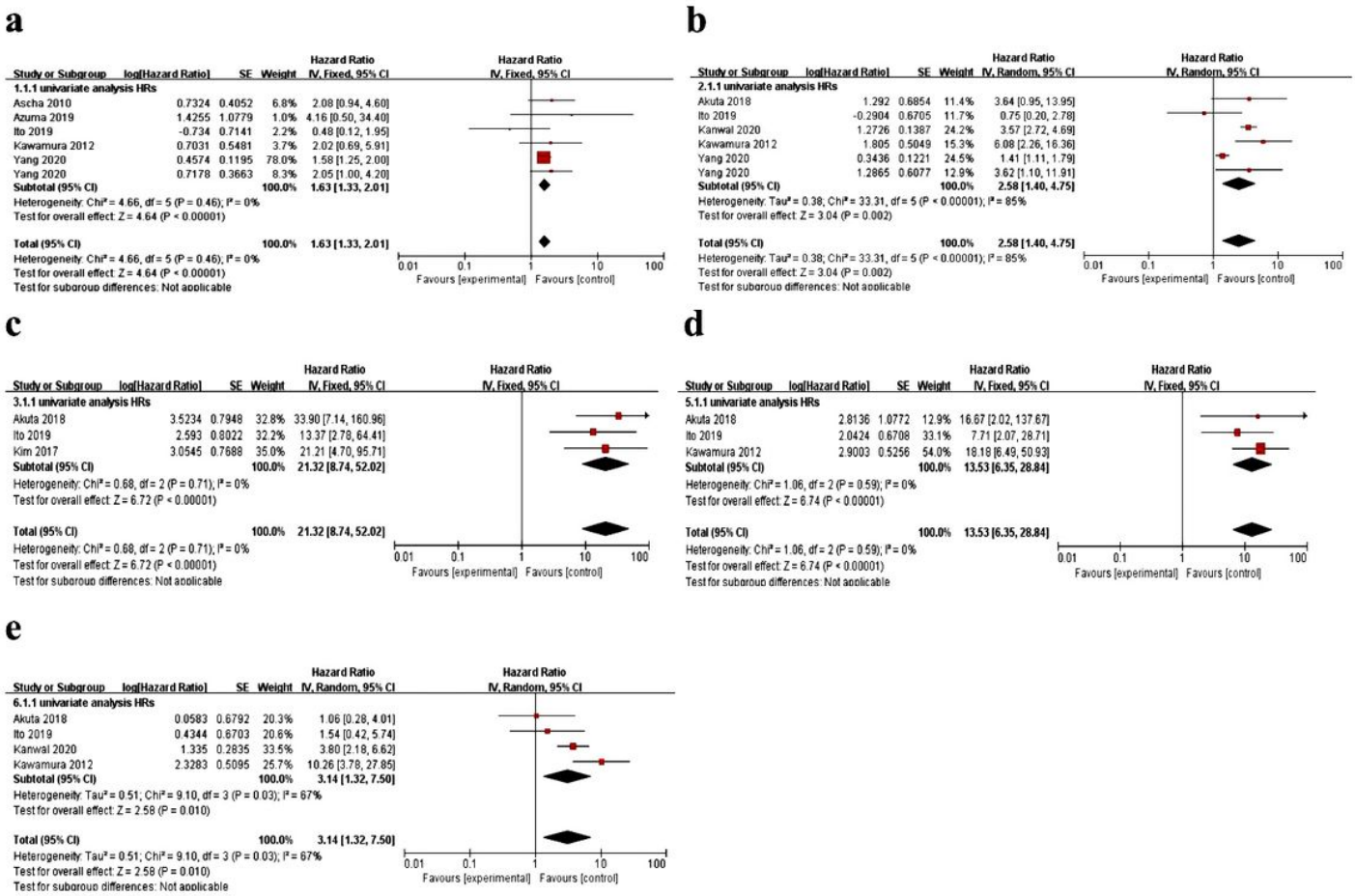

Figure 3 （a） Forest plot of pooled univariate analysis HRs in male. (b) Forest plot of pooled univariate analysis HRs in diabetes. (c) Forest plot of pooled univariate analysis HRs in advanced fibrosis. (d) Forest plot of pooled univariate analysis HRs in low platelet count. (e) Forest plot of pooled univariate analysis HRs in hypertension.

Figure 3

See image above for figure legend

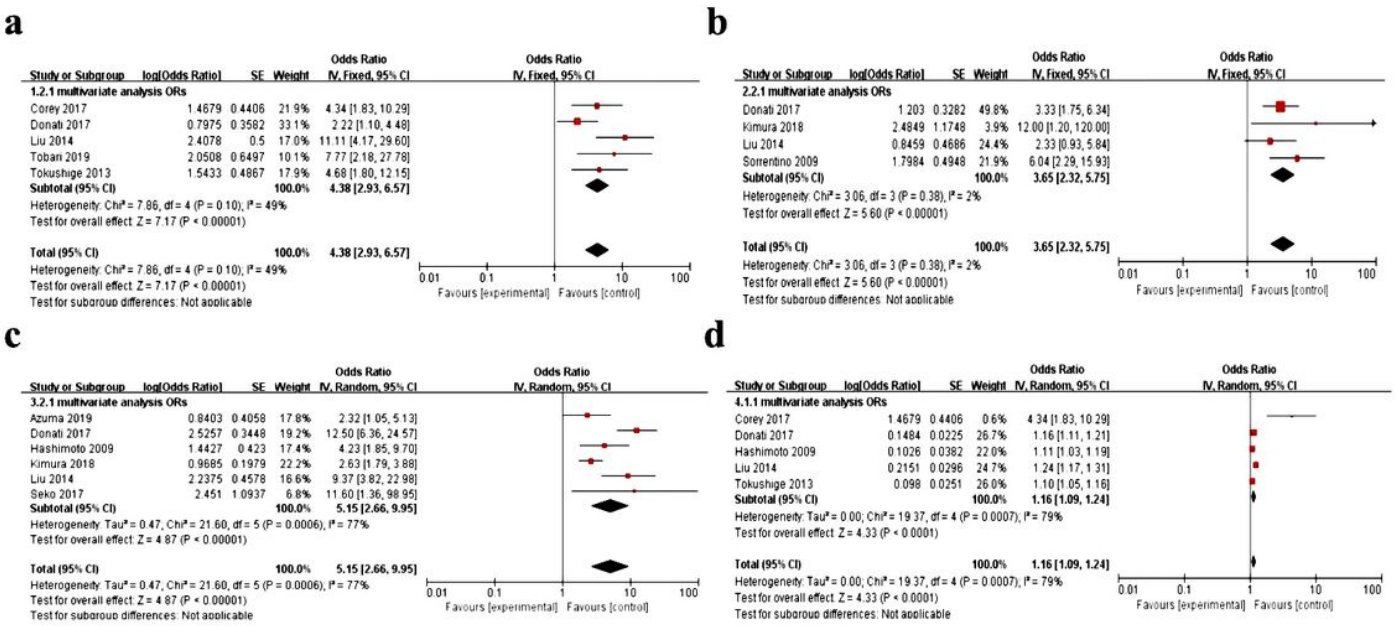

Figure 4 （a）Forest plot of pooled multivariate analysis ORs in male. (b) Forest plot of pooled multivariate analysis ORs in diabetes. (c) Forest plot of pooled multivariate analysis ORs in advanced fibrosis. (d) Forest plot of pooled multivariate analysis ORs in older age.

Figure 4

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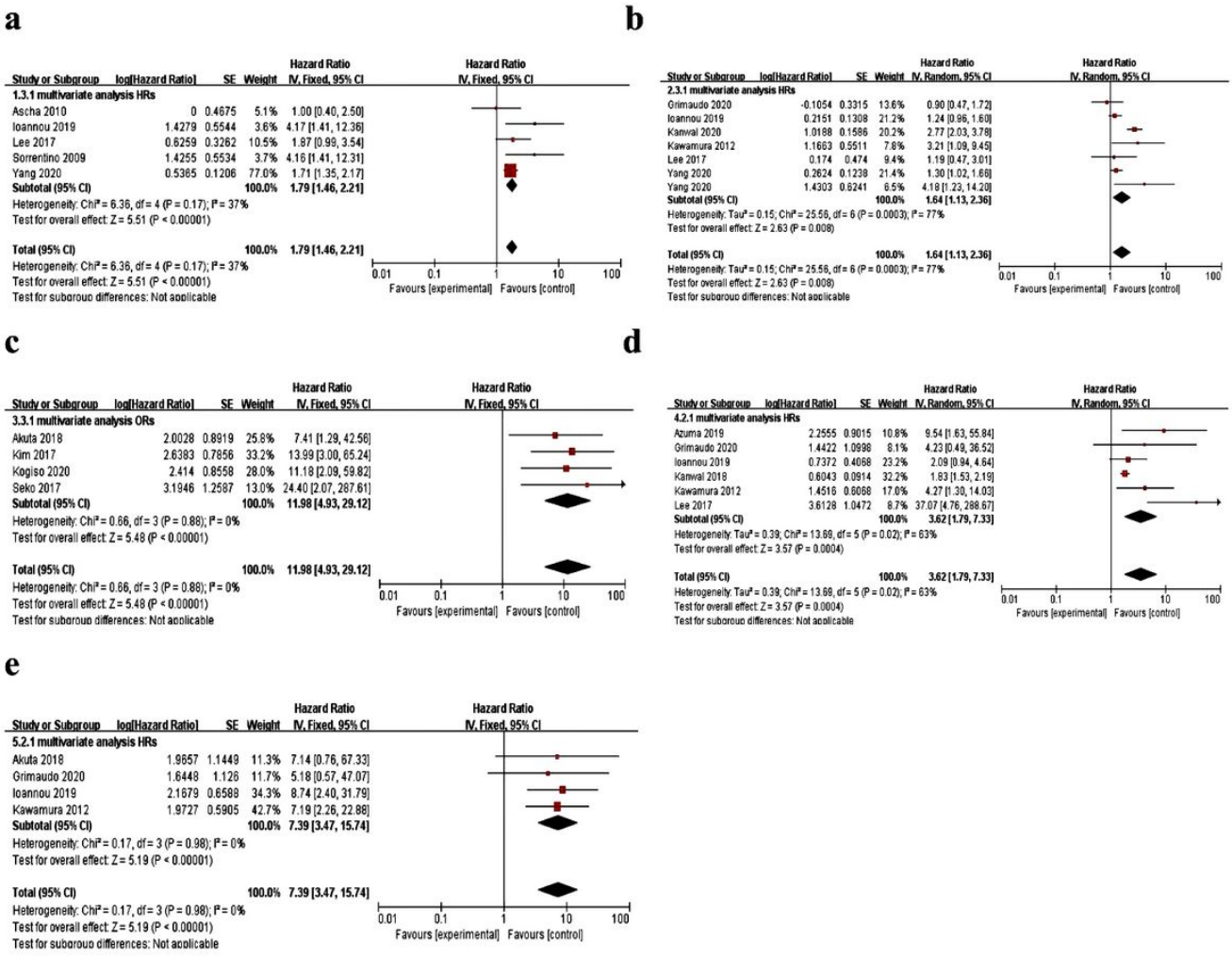

Figure 5 （a）Forest plot of pooled multivariate analysis HRs in male. (b) Forest plot of pooled multivariate analysis HRs in diabetes. (c) Forest plot of pooled multivariate analysis HRs in advanced fibrosis. (d) Forest plot of pooled multivariate analysis HRs in older age. (e) Forest plot of pooled multivariate analysis HRs in low platelet count.

Figure 5

See image above for figure legend

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Suppl.Table1Searchstrategy.docx
- Suppl.Table2Checklist.docx
- Suppl.Table3Biasassessment.docx