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# Incidence of Hepatocellular Carcinoma in Patients With Nonalcoholic Fatty Liver Disease: A Systematic Review, Meta-analysis, and Meta-regression

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**BACKGROUND & AIMS:** **Nonalcoholic fatty liver disease (NAFLD) may be a risk factor for hepatocellular carcinoma (HCC), but the extent of this association still needs to be addressed. Pooled incidence rates of HCC across the disease spectrum of NAFLD have never been estimated by meta-analysis.**

**METHODS:** **In this systematic review, we searched Web of Science, Embase, PubMed, and the Cochrane Library from January 1, 1950 through July 30, 2020. We included studies reporting on HCC incidence in patients with NAFLD. The main outcomes were pooled HCC incidences in patients with NAFLD at distinct severity stages. Summary estimates were calculated with random-effects models. Sensitivity analyses and meta-regression analyses were carried out to address heterogeneity.**

**RESULTS:** **We included 18 studies involving 470,404 patients. In patients with NAFLD at a stage earlier than cirrhosis, the incidence rate of HCC was 0.03 per 100 person-years (95% confidence interval [CI], 0.01–0.07; $I^2 = 98\%$). In patients with cirrhosis, the incidence rate was 3.78 per 100 person-years (95% CI, 2.47–5.78; $I^2 = 93\%$). Patients with cirrhosis undergoing regular screening for HCC had an incidence rate of 4.62 per 100 person-years (95% CI, 2.77–7.72; $I^2 = 77\%$).**

**CONCLUSIONS:** **Patients with NAFLD-related cirrhosis have a risk of developing HCC similar to that reported for patients with cirrhosis from other etiologies. Evidence documenting the risk in patients with nonalcoholic steatohepatitis or simple steatosis is limited, but the incidence of HCC in these populations may lie below thresholds used to recommend a screening. Well-designed prospective studies in these subpopulations are needed. The protocol for this systematic review is registered in the Prospero database (registration number CRD42018092861).**

*Keywords:* Hepatocellular Carcinoma; Incidence; Meta-analysis; Nonalcoholic Fatty Liver Disease.

Epidemiologic data indicate an alarming rise in the global prevalence of NAFLD, which has now become one of the most common forms of chronic liver disease. Predictions suggest that the burden of NAFLD will grow further in the next decades.[1] These epidemiologic trends have made NAFLD-induced cirrhosis a leading cause of HCC.[2–4] The global incidence of HCC related to NAFLD is projected to increase from 47% in 2016 to 130% in 2030.[5] However, because NAFLD encompasses a wide spectrum of disease, the precise extent of the association between NAFLD and HCC remains unclear.[6,7] Although the development of cirrhosis appears to be a major driver of hepatocarcinogenesis (independently from the underlying liver disease), the risk of developing HCC in other subpopulations of patients with NAFLD needs to be better addressed.[8] Some evidence indicates that patients with NAFLD may develop HCC at stages

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*Abbreviations used in this paper:* CI, confidence interval; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PY, person-year.


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## What You Need to Know

### Background

The risk of hepatocellular carcinoma (HCC) in patients with nonalcoholic fatty liver disease (NAFLD) has been reported in various studies. This systematic review and meta-analysis evaluated the pooled incidence of HCC in various populations of patients with NAFLD.

### Findings

On the basis of the current results, the incidence of HCC in patients with NAFLD at a stage earlier than cirrhosis is 0.03 per 100 person-years (95% CI, 0.01–0.07). In patients with cirrhosis, the rate is 3.78 per 100 person-years (95% CI, 2.47–5.78). Patients with cirrhosis undergoing regular screening for HCC have an incidence rate of 4.62 per 100 person-years (95% CI, 2.77–7.72). Results were highly heterogeneous.

### Implications for patient care

Patients with nonalcoholic fatty liver disease (NAFLD)-related cirrhosis have a risk of developing hepatocellular carcinoma (HCC) similar to that reported for patients with cirrhosis from other etiology. Evidence documenting the risk in patients with nonalcoholic steatohepatitis (NASH) or simple steatosis is limited and highly heterogeneous.

earlier than cirrhosis.[9,10] However, those studies did not take into consideration whether patients were enrolled in HCC surveillance programs.

In chronic hepatitis B for instance, there is some evidence to support that screening for HCC is cost-effective in high-risk carriers without cirrhosis, when the rate of HCC exceeds 0.2% per year.[11,12] As for NAFLD, European practice guidelines recommend regular surveillance for HCC in patients with cirrhosis when the annual rate of HCC exceeds 1.5% per year.[13] The American Association for the Study of Liver Disease cautiously suggests that the latter threshold may also be applicable to patients with non-cirrhotic NAFLD.[12] However, as of today, it is unknown whether non-cirrhotic patients with NAFLD truly carry a risk of developing HCC that lies above either of these thresholds. Therefore, the benefit of surveillance in non-cirrhotic NAFLD patients remains uncertain.

Two previous systematic reviews by White et al[14] and Stine et al[15] have looked at the association between NAFLD and HCC. Despite their seminal work in 2012, White et al did not provide quantitative pooling of the results by meta-analysis. More importantly, a large amount of newer evidence has been published since 2012. Among other findings, the meta-analysis by Stine et al reported 2.61 times higher incidence of HCC in non-cirrhotic NAFLD in comparison with patients with liver disease of other etiology. Although this is an important indication of the depth of association between HCC and NAFLD, the result does not inform health care stakeholders about the absolute incidence of HCC in the NAFLD population. Furthermore, neither of the 2 above-mentioned systematic reviews specifically addressed the impact of screening, which is a key public health issue. Our group also published the results of a conference-related qualitative literature review in 2019,[16] but we believed that a more thorough systematic review was needed, especially considering that the public health awareness with regard to the NAFLD epidemic grows bigger, and that several important studies have been published in the meantime. In the current systematic review and meta-analysis, we aimed to estimate the pooled incidence rates of HCC across the spectrum of NAFLD and to evaluate the impact of surveillance on the detection rate.

## Methods

### *Search Strategy and Selection Criteria*

The protocol for this systematic review is registered in the Prospero database (registration number CRD42018092861). The reviewing process was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. We searched Web of Science, Embase, PubMed, and the Cochrane Library from January 1, 1950 through July 30, 2020 by formulating keyword searches. The exact query formulated in Web of Science was as follows: "(TS=(nonalcoholic fatty liver OR nafld OR nbnc OR nafl OR non alcoholic fatty liver disease OR non-alcoholic fatty liver OR non-alcoholic fatty liver disease OR nonalcoholic fatty liver disease OR non-alcoholic steatohepatitis OR nonalcoholic steatohepatitis OR non-alcoholic steato-hepatitis OR non-alcoholic steato hepatitis OR non alcoholic steatohepatitis OR non alcoholic steato-hepatitis OR non alcoholic steato hepatitis OR nonalcoholic steato-hepatitis OR nonalcoholic steato- hepatitis OR fatty liver disease OR fatty liver OR non-alcoholic steatosis OR nonalcoholic steatosis OR non alcoholic steatosis OR non viral hepatitis OR non-viral hepatitis OR non b non c OR non-b non-c OR nash OR steato-hepatitis OR steatohepatitis OR liver steatosis OR steatosis OR metabolic syndrome OR liver fat infiltration) AND TS=(liver cell carcinoma OR hepatic carcinoma OR liver cell carcinoma OR hepatic cell carcinoma OR hepatocarcinoma OR hepatocellular carcinoma OR hepatoma OR liver carcinoma OR primary liver carcinoma OR malignant hepatoma OR hcc OR carcinoma of the liver))". Keyword combinations used in other databases are reported in the Supplementary Material. Duplicate reports were eliminated by scrutinizing the list of aggregated reports. In addition, we manually scanned the reference list of previously published systematic reviews[14,15] and that of articles retrieved from the literature search.

Two reviewers (LO, BC) independently selected potentially relevant studies on the basis of title and abstract reading. Full-text articles were then gathered and assessed for eligibility by the same 2 independent reviewers. In case of discrepancies, consensus was reached after discussion with senior authors (CT, MR). To be eligible, studies had to report within a study population of patients diagnosed with NAFLD (all other etiologies including cryptogenic cirrhosis were excluded), the number of incident HCC cases over time, or the cumulative incidence. We excluded studies where patients were already diagnosed with HCC when entering the study; studies not reporting the follow-up period; studies assessing the recurrence of HCC after liver resection, transplantation, or ablative therapies; studies that did not specifically report on HCC; and studies that did not specify whether and how alcohol intake was accounted for. We also excluded conference abstracts, letters, and editorials. We did not search for unpublished reports or the grey literature.

### Outcome of Interest

The outcome of interest was the pooled incidence rate of HCC, as estimated in patients at distinct stages of NAFLD severity and according to their clinical management. In other words, the incidence rates of HCC were calculated for (1) patients with non-cirrhotic NAFLD, (2) patients with NAFLD-induced cirrhosis, (3) patients with NAFLD-induced cirrhosis enrolled in a dedicated screening program, and (4) those not undergoing regular surveillance.

### Data Analysis

Two authors extracted data by using a preestablished form. In addition to the usual bibliometric variables, information on the following variables was also collected: duration of inclusion; study design; methods used to diagnose NAFLD and HCC; median follow-up; percentage of patients with simple steatosis, NASH, and cirrhosis; number of incident HCC cases; enrollment (and structure of) a systematic HCC screening program; age; sex; body mass index; presence of diabetes and dyslipidemia; alanine aminotransferase and aspartate aminotransferase serum levels; Model for End-Stage Liver Disease score; and platelet count.

Critical appraisal was done independently by 2 reviewers (LO, BC) using the National Institutes of Health Quality Assessment Tool for observational cohort and cross-sectional studies.[17] Briefly, this tool checks for the presence of 14 core quality components of observational studies, including population sampling, definition of both the exposure and the outcome, timeframe for the exposure to exert an effect on the outcome, presence of the exposure variable (NAFLD) before the outcome (HCC), blinding of outcome assessors, and losses to follow-up. On the basis of these components, each study is rated as good, fair, or poor in quality (indicating low, moderate, and high risk of bias, respectively). When means and standard deviations were not reported, we estimated them from medians and percentiles.[18]

The number of cases and the person-years (PYs), calculated as the product of the total number at risk and the follow-up from individual studies, were used to compute the pooled number of incident HCC cases per 100 PYs of follow-up, and their 95% confidence intervals (CIs) were estimated using the random-effects model described by Der Simonian and Laird[19] with the metarate command of R. Heterogeneity was evaluated by means of the $I^2$ statistic, and values of $I^2$ of 25%, 50%, and 75% were considered to indicate low, moderate, and high heterogeneity, respectively.[20] A $\chi^2$ heterogeneity test was performed to evaluate the statistical significance of the lack of homogeneity, considering $P < .100$ as threshold.[21]

A funnel plot was constructed to assess publication bias. Heterogeneity was investigated through several approaches. First, we conducted sensitivity analyses, looking at the impact of factors such as (1) the diagnostic tool used to establish the diagnosis of NAFLD, (2) the epidemiologic design, (3) the methodological quality, and (4) the geographical location of the included studies. We also performed leave-one-out analyses to evaluate whether a single study could have a marked impact on overall heterogeneity. Next, we used random-effects meta-regression models to evaluate the impact of baseline covariates on the calculated heterogeneity. Whenever $I^2$ was greater than 50%, date of publication ($\leq$2010 versus $>$2010), study duration, age, sex, presence of diabetes, Model for End-Stage Liver Disease score, platelet count, and aspartate aminotransferase and alanine aminotransferase blood levels were included as covariates.

Between-reviewer agreement in terms of methodological quality and decision to include studies was assessed by means of Kendall and kappa coefficients, respectively. All statistical analyses were performed using RStudio Team 2018 software (RStudio: Integrated Development for R; RStudio, Inc, Boston, MA), and the level of significance was set at the two-sided 5%. Meta-regression was performed using the metareg command of R.

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to the study data and reviewed and approved the final manuscript.

## Results

### Literature Search and Critical Appraisal

After duplicate removal, our literature searches yielded 10,263 articles. We screened 139 potentially

relevant reports, reviewed 89 articles in full-text, and finally included 18 studies in the analysis.[22–39] Between-reviewer agreement for the inclusion process was 0.92 (95% CI, 0.84–0.99), as assessed by the kappa coefficient. Details of the inclusion process and reasons for exclusion are shown in Figure 1. The characteristics of the included studies are summarized in Table 1. Reasons for excluding the 71 out the 89 selected articles are reported in the Supplementary Table 1.

The 18 studies enrolled 470,404 patients with a diagnosis of NAFLD. Overall, 20% of the whole population were women. However, when we excluded the study by Kanwal et al,[30] which analyzed data of 296,707 U.S. military veteran personnel, the proportion of women rose to 55%. The diagnosis of NAFLD and/or NASH was based on liver histology in 5 studies,[25,27,29,36,39] whereas other reports used a combination of liver imaging and blood level of aminotransferases[22,24,28,33,35] or ultrasound only.[23,31,32] Of note, the study by Adams et al[22] reported separate analyses for a subgroup of patients with histologically proven NASH lesions.

There was variability in terms of the presence of NASH and NAFLD-induced cirrhosis across the included studies (Supplementary Table 2). As for cancer screening, patients were enrolled in dedicated surveillance programs for HCC in 10 studies, using repeated ultrasound imaging,[25,31,35] combined ultrasound and blood level of alpha-fetoprotein,[23,27,33,39,40] computed tomography,[24] or a combination of these approaches.[37] The presence of conditions that are commonly associated with NAFLD (such as diabetes, hypertension, and obesity) is reported in Table 2.

Critical appraisal, as assessed by the National Institutes of Health Quality Assessment Tool (Supplementary Table 3), indicated that one study had high risk of bias,[23] 11 moderate risk,[26–35,39] and 6 low risk.[22,24,25,36–38] Between-reviewer concordance was 0.72 (95% CI, 0.41–0.99), as assessed by the Kendall coefficient.

### *Quantitative Synthesis of the Incidence of Hepatocellular Carcinoma in Patients With Nonalcoholic Fatty Liver Disease*

When gathering studies that included at least some patients with cirrhosis, the estimated pooled incidence rate of HCC was 2.39 per 100 PYs (95% CI, 1.40–4.08; $I^2 = 93\%$; heterogeneity test $P < .01$; Figure 2*A*). To estimate more specifically the risk of HCC carried by patients with NAFLD-related cirrhosis, we restricted the analysis to studies that only included patients with established cirrhosis.[24,27–29,33,35,38] In these studies, the pooled incidence of HCC was 3.78 per 100 PYs (95% CI,

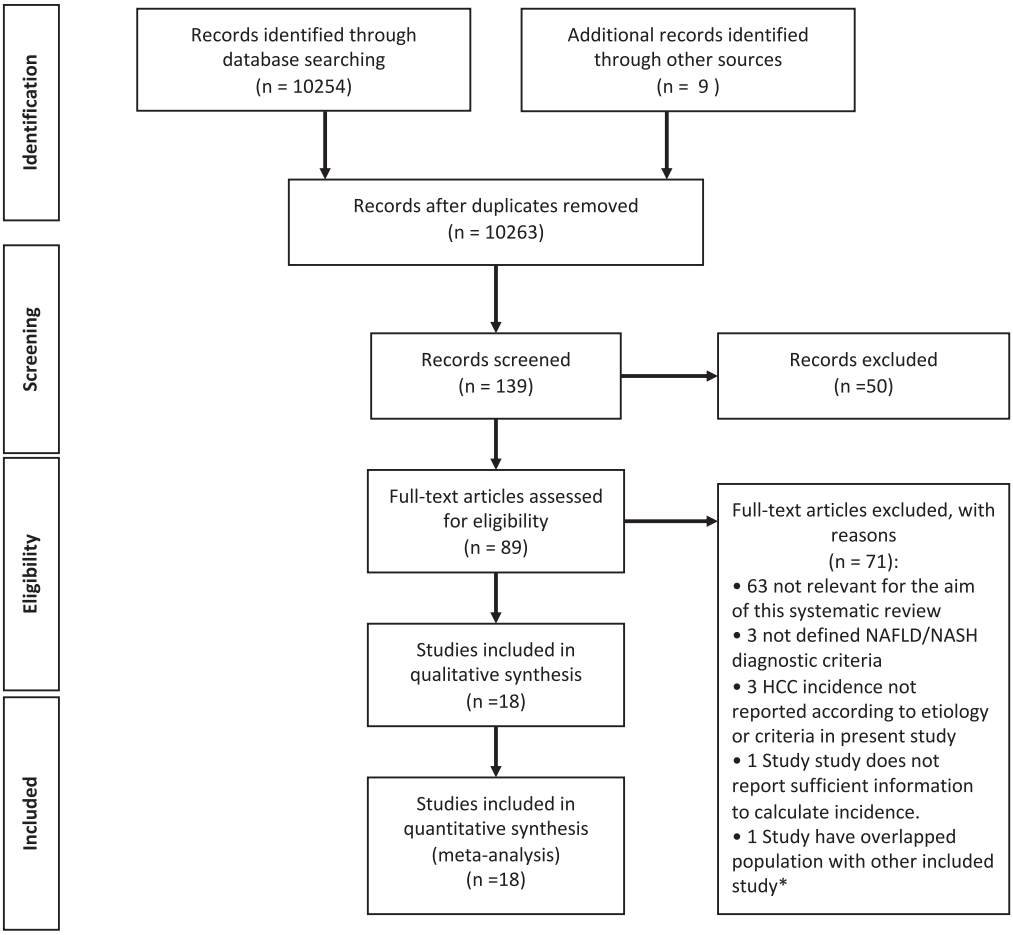


**Figure 1.** PRISMA flow diagram of study selection. HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

**Table 1.** Characteristics of Studies

| First author | Year of publication | Country | Study design | Period of inclusion | Screening type | NAFLD-patients with cirrhosis (%) |
|---|---|---|---|---|---|---|
| Hui | 2003 | Australia | Prospective | NA | No screening | 100 |
| Adams | 2005 | USA | Retrospective | 1980–2000 | No screening | NA |
| Ekstedt | 2006 | Sweden | NA | 1988–1993 | No screening | 4.5 |
| Hashimoto | 2009 | Japan | Prospective | 1990–2007 | US + AFP | 35.8 |
| Yatsuji | 2009 | Japan | Prospective | 1990–2006 | US + AFP | 100 |
| Ascha | 2010 | USA | Retrospective | 2003–2007 | Others | 100 |
| Bhala | 2011 | International | Prospective | 1984–2006 | US | 52.2 |
| Arase | 2012 | Japan | Retrospective | 1994–2007 | US + AFP | NA |
| Kawamura | 2012 | Japan | Retrospective | 1997–2010 | US | NA |
| Kodama | 2013 | Japan | Retrospective | 1990–2010 | US + AFP | 100 |
| Önnerhag | 2014 | Sweden | Prospective | 1974–1992 | No screening | 25 |
| Hsiang | 2015 | New Zealand | Retrospective | 2000–2011 | No screening | 100 |
| Kim | 2017 | South Korea | Retrospective | 2004–2005 | No screening | NA |
| Lee | 2017 | Taiwan | Retrospective | 1998–2012 | No screening | NA |
| Marot | 2017 | Switzerland | Prospective | 1995–2014 | US | 100 |
| Kanwal | 2018 | USA | Retrospective | 2004–2008 | NA | 0.5 |
| Alexander | 2019 | International | Retrospective | Before 2016 | NA | 0 |
| Yang | 2020 | USA | Retrospective | 2006–2015 | NA | 100 |

AFP, alpha-fetoprotein; NA, not available; NAFLD, nonalcoholic fatty liver disease; US, ultrasound.

2.47–5.78; $I^2 = 81\%$; heterogeneity test $P < .01$; Figure 2*B*). The pooled incidence of HCC in patients with cirrhosis enrolled in a HCC screening program[24,27,33,35] was 4.62 per 100 PYs (95% CI, 2.77–7.72; $I^2 = 77\%$; heterogeneity test $P < .01$; Figure 2*C*). In contrast, the pooled incidence rate of HCC was markedly lower (2.35 per 100 PYs) when we pooled studies that included patients not undergoing regular surveillance (95% CI, 0.99–5.61; $I^2 = 56\%$; heterogeneity test $P < .01$; Figure 2*D*). When looking at those 3 studies[22,30,37] reporting the incidence of HCC in patients with non-cirrhotic NAFLD, we found that the incidence rate of HCC in non-cirrhotic patients was 0.03 per 100 PYs (95% CI, 0.01–0.07; $I^2 = 98\%$; heterogeneity test $P = .02$; Figure 2*E*).

### *Investigating Heterogeneity*

Next, because between-study heterogeneity was very high in most of our meta-analyses, we carried out several sensitivity analyses (Supplementary Table 4), restricting data aggregation according to potential sources of heterogeneity. Despite modifying the calculated effect sizes, these factors did not allow us to remove residual heterogeneity. Meta-regression analyses (Figure 3) were performed considering the duration of patient inclusion in the individual studies, patient age, proportion of men, percentage of patients with diabetes, and date of publication. The meta-regression considering the date of publication revealed a coefficient $P = .04$ (Supplementary Table 5). However, even after allowing for this factor, global heterogeneity (considering all the remaining confounders) still remained very high ($I^2 = 94\%$). Other variables evaluated by meta-regression did not reach statistical significance (Figure 3, Supplementary Table 5). We finally performed a leave-one-out sensitivity analysis (Supplementary Table 6) on those studies reporting on the incidence of HCC in patients with cirrhosis, but this strategy only marginally reduced heterogeneity ($I^2 > 90\%$). We did not find evidence of publication bias, as assessed by using a funnel plot (Supplementary Figure 1).

## Discussion

In this systematic review and meta-analysis, we provide a comprehensive assessment of the incidence of HCC in various subpopulations of patients with NAFLD, taking into account the impact of HCC screening. When looking at studies that only included patients with cirrhosis, the incidence rate of HCC was 3.78 per 100 PYs (95% CI, 2.47–5.78), a finding of similar magnitude to

**Table 2.** Patient Characteristics

| First author | Year of publication | Age, *y* (mean ± SD) | Gender (male-%) | Obesity (%) | BMI, $kg/m^2$ (mean ± SD) | Diabetes (%) | Hypertension (%) | Dyslipidemia (%) |
|---|---|---|---|---|---|---|---|---|
| Hui | 2003 | 52.6 ± 13.6 | 30 | 70 | 32.0 ± 5.1 | 65 | 48 | 30 |
| Adams | 2005 | 49 ± 15 | 49 | 71 | 33.5 ± 6.5 | 26 | 36 | 23 |
| Ekstedt | 2006 | 61 ± 11 | 70 | 33 | 29.1 ± 4.7 | 57 | 94 | 40 |
| Hashimoto | 2009 | NA | NA | NA | NA | NA | NA | NA |
| Yatsuji | 2009 | 62.7 ± 13.2 | 43 | 24 | 27.8 ± 5.4 | 68 | 47 | 34 |
| Ascha | 2010 | 56 ± 7.6[a] | 44.1 | NA | 34.7 ± 5.3[a] | 73.1 | NA | NA |
| Bhala | 2011 | 54.7 ± 11.6 | 39.7 | NA | 32.8 ± NA | 50.6 | 44.1 | NA |
| Arase | 2012 | 62.5 ± 9.5 | 75 | NA | 25.1 ± 2.6 | NA | 17.4 | NA |
| Kawamura | 2012 | 52.7 ± 46.7 [a] | 87.7 | NA | 28.6 ± 21.6[a] | 8.2 | 12.9 | NA |
| Kodama | 2013 | 63.5 ± 12.9 | 32 | 74 | 27.7 ± 5.3 | 58 | 54 | 42 |
| Önnerhag | 2014 | 47.5 ± 7.3 | 72.2 | NA | 27.1 ± 12.4[a] | 41.7 | 50 | 33.3 |
| Hsiang | 2015 | 63 ± 12 | 50 | NA | NA | NA | NA | NA |
| Kim | 2017 | 50.1 ± 9.7 | 71.1 | NA | 25.7 ± 2.6 | 16.2 | 32.3 | NA |
| Lee | 2017 | 52.9 ± 16.9 [a] | 52.6 | NA | NA | 37 | 55.9 | 23.3 |
| Marot | 2017 | 63 ± 20 [a] | 51 | NA | 31 ± 1.5[a] | 73 | NA | NA |
| Kanwal | 2018 | 55.4 ± NA | 94.4 | NA | 30.7 ± NA | 29.9 | 70.2 | NA |
| Alexander | 2019 | 55.8 (13.6) | 52.7 | NA | NA | 19.8 | 42.2 | 16.9 |
| Yang | 2020 | 61.5 (NA) | 41 | NA | 37.2 ± NA | 71.5 | 73.4 | 74.9 |

BMI, body mass index; NA, not available; SD, standard deviation.
[a]Estimated.

the rates reported in patients with cirrhosis of other etiologies.[41,42] It is noteworthy that this rate (and its lower CI limit) lie above the 1.5% annual risk threshold usually accepted to recommend regular HCC surveillance.[12] We further carried out separate analyses for studies documenting the enrollment of patients in dedicated surveillance programs, and we found that screening raised the incidence rate of HCC to 4.62 per 100 PYs (95% CI, 2.77–7.72). On the basis of these results, the current meta-analysis strongly supports the implementation of regular screening programs for patients with NAFLD-related cirrhosis.

The novelty of the present meta-analysis revolves around patients with non-cirrhotic NAFLD, who are, in daily clinical care, commonly deemed to be at a higher risk of developing HCC in comparison with patients with chronic liver diseases of other etiologies. In this regard, the current results challenge this assumption, because we found a pooled incidence rate for HCC of 0.03 per 100 PYs (95% CI, 0.01–0.07) among patients with non-cirrhotic NAFLD. Although it is not based on the same measure of association, this finding contrasts with an interesting study by Piscaglia et al,[43] who documented that nearly 50% of NAFLD-associated HCCs arise within non-cirrhotic liver parenchyma. Although our estimate of the incidence of HCC in patients with non-cirrhotic NAFLD may have been pushed toward the null because of the lack of screening in real-life clinical care, one may debate whether the study by Piscaglia et al was not prone to some selection bias that may have contributed to reveal a markedly elevated proportion of HCC in non-cirrhotic livers.[43] Of note, the pooled incidence rate of 0.03 per 100 PYs in our study was a result from the recruitment of a broad-spectrum disease (from simple steatosis forms to non-cirrhotic steatohepatitis and eventually early fibrosis) into a single category. The specific estimation of incidence rates of HCC at distinct pre-cirrhotic NAFLD stages could not be assessed, and this limitation calls for further research in these categories of patients.

Most of the results of the current meta-analysis are characterized by a high heterogeneity, likely because of the clinical variability of the individual studies included herein (for instance in terms of the methods used to define NAFLD, the strategy used to diagnose HCC, or the health care setting in which patients were clinically assessed). More importantly, such heterogeneity may also reflect the remarkable biological diversity of the pathogenesis of NAFLD at stages earlier than cirrhosis. This observation deserves a few comments. First, although debatable,[44] it is likely that the variability in the risk of developing HCC in non-cirrhotic patients may be

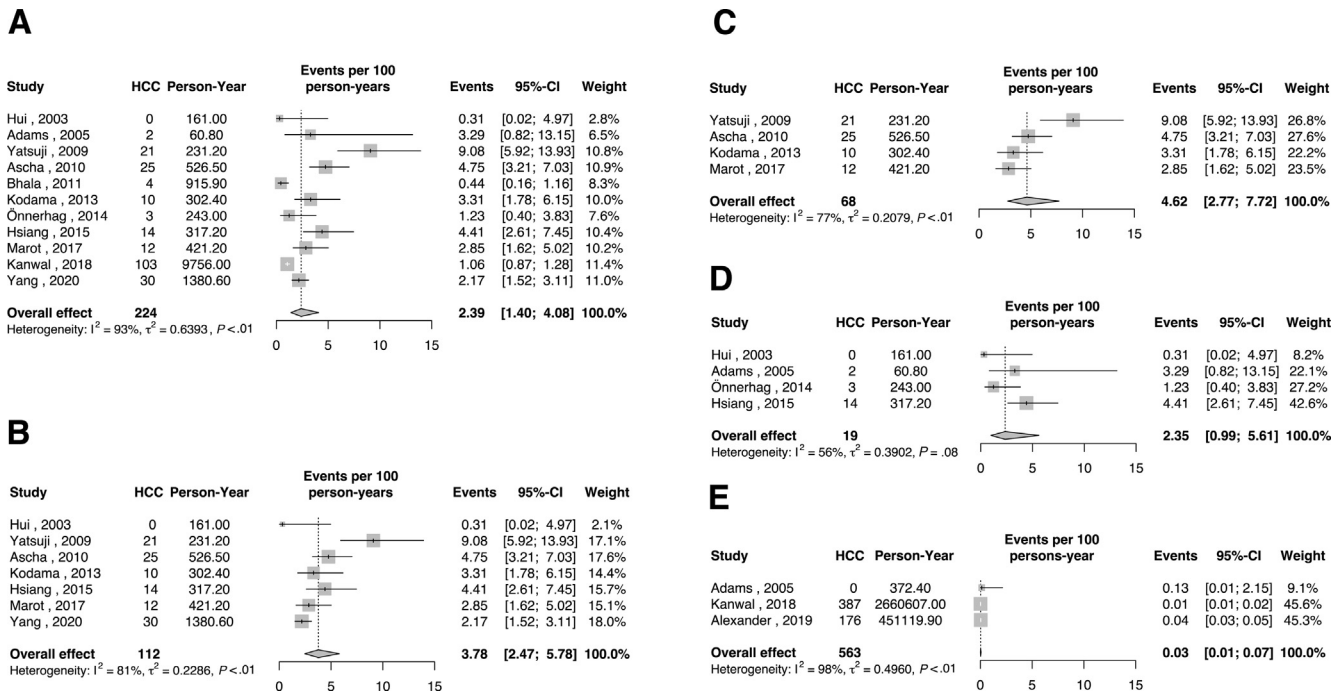


**Figure 2.** Meta-analyses of incidence of hepatocellular carcinoma in patients with nonalcoholic fatty liver disease, as depicted by forest plots. *Each square* represents the effect estimate of a study, along with its 95% confidence interval. Surface of the square summarizes the weight of that individual study in the meta-analysis. *Vertical dashed line* depicts the pooled effect estimate. (*A*) Studies that included at least some patients with cirrhosis. (*B*) Studies that included only patients with cirrhosis. (*C*) Studies that included patients with cirrhosis who were enrolled in a screening program. (*D*) Studies that included patients who did not undergo regular surveillance. (*E*) Pooled incidence rate in non-cirrhotic patients. CI, confidence interval; HCC, hepatocellular carcinoma.

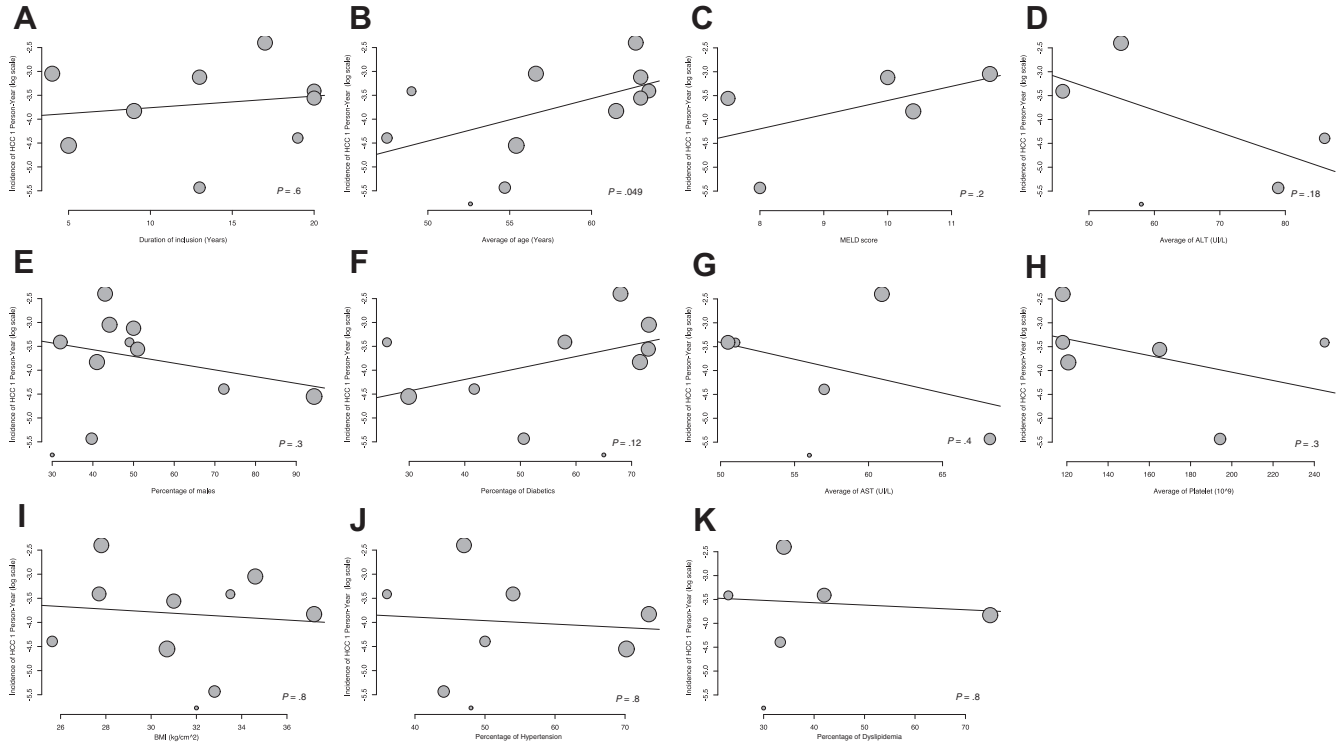


**Figure 3.** Meta-regression analyses, as depicted by *bubble plots*, looking at impact of various sources of heterogeneity (x-axis) on calculated effect sizes (y-axis). (*A*) Duration of inclusion, (*B*) age of study population, (*C*) MELD score, (*D*) alanine aminotransferase levels, (*E*) percentage of males, (*F*) percentage of patients with diabetes, (*G*) aspartate aminotransferase levels, (*H*) platelet levels, sex of study population, (*I*) body-mass index, (*J*) percentage of patients with hypertension, and (*K*) percentage of patients with dyslipidemia.

ascribable to the presence and the extent of hepatic inflammation and fibrosis rather than to the severity of liver steatosis.[45] Second, one may speculate on the existence of potential additional risk factors that would contribute to promoting hepatocarcinogenesis in those patients. One such risk factor could be exaggerated gut leakiness, where translocation of bacterial debris and other toxic products from the gut lumen to the portal circulation (for instance, during repeated bouts of spontaneous bacterial peritonitis) may promote liver inflammation and carcinogenesis via the engagement of innate immunity receptors by damage- and/or pathogen-associated molecular patterns.[46] Taken together, these data reinforce the idea that the "host condition" is not sufficient to trigger carcinogenesis, but that such host condition could rather be disrupted on exposure to specific risk factors. Notably, whereas some authors have proposed to take into account variables such as the PNPLA3 rs738409 C>G gene polymorphism,[47,48] the impact of additional genetic or environmental factors and the gut microbiome could not be assessed in the current meta-analysis.

Another important aspect of the current work regards tumor surveillance. Although screening for HCC is effective at identifying HCC (potentially at an early, curable stage) as evidenced by the current results, biannual evaluation is difficult to implement.[49] Even in high-income countries, it has been shown that up to two-thirds of patients do not benefit from adequate biannual screenings,[50] putting them at risk of developing HCC during exaggeratedly prolonged intervals. Moreover, evidence indicates that screening programs carry an economic burden on the community,[51] and that regular surveillance comes at an emotional cost for patients.[52,53] Therefore, the World Health Organization recommendations state that cancer screening strategies should be both cost-effective and targeted toward very well-defined populations to minimize false-positive testing and avoiding psychological harm from such a public health policy.[54] On the basis of the currently assessed evidence, it could be assumed that our estimation of the incidence rate of HCC in non-cirrhotic livers of 0.03 per 100 PYs (95% CI, 0.01–0.07) does not support HCC screening in non-cirrhotic patients. This incidence reflected the rate of HCC among a heterogeneous group of patients, including those with simple steatosis and different degrees of fibrosis. This is of utmost relevance considering that those patients with more advanced fibrosis have been suggested to be at higher risk of HCC.[55] In addition, it is important to remember that our study aimed to establish the current incidence of HCC in these populations and not to suggest the benefits of a screening program for HCC. The incidence of HCC in specific populations is key for such an assessment, but it has to incorporate the data about life expectancy and competing risk of death posed by severe comorbidities (cardiovascular disease and non-liver cancer) as well as cost.

There are several strengths to our systematic review and meta-analysis. Indeed, it provides a comprehensive, up-to-date assessment of currently available evidence. Nevertheless, the current results, although heterogenous, challenge a dogma whereby patients with NAFLD, even at early disease stages, may be particularly prone to HCC and point out that there is no strong evidence until now to support the screening of patients with non-cirrhotic NAFLD. Specifically, this is an attempt to report distinct estimates of the incidence of HCC in various subpopulations of patients with NAFLD by meta-analysis. Finally, we were cautious in including only those studies clearly identifying NAFLD cases, and we excluded studies with doubtful diagnoses (eg, non-A, non-B hepatitis).

Our study also has some limitations. First, we could not gather quantitative information on the risk of HCC in non-cirrhotic patients with simple nonalcoholic fatty liver, NASH, or F1–F2 liver fibrosis from the current literature. Second, we performed sensitivity analyses looking at the impact of tumor screening only on the basis of those studies that clearly stated whether patients were adhering (or not) to a dedicated screening program. Therefore, we could not use studies that did not evaluate tumor surveillance. Third, despite investigating heterogeneity through various approaches, we did not obtain homogenous estimates of the incidence in the studied populations. Finally, because of the study design, we could not directly assess the impact of factors (such as metabolic risk factors or sex) beyond meta-regression.

In conclusion, this meta-analysis of observational studies provides pooled estimates of the incidence of HCC in patients with NAFLD. Even with high heterogeneity, our results support that HCC surveillance is beneficial in patients with NAFLD-related liver cirrhosis. By highlighting the scarcity of evidence on the value of screening for HCC in patients with non-cirrhotic NAFLD, the current systematic review should be used as the rationale for the design of a new risk-scoring tool (such as, by analogy, the PAGE-B score for patients with chronic hepatitis B[56]). If shown accurate, such a tool would help in the tailoring of personalized surveillance programs for patients with NAFLD.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2021.05.002.

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## Supplementary Material

### *Detailed Search Strategy*

Database searches were run on May 3, 2018 and repeated on July 30, 2020. Altogether, after duplicate exclusion, n = 10,254 records were screened. Ten thousand one hundred fifteen studies could be excluded by deemed irrelevant based on the title, leaving 139 studies that were more thoroughly screened. Fifty studies were removed, mostly because they obviously did not fit to our inclusion criteria (eg, histopathologic study, case series descriptions without incidence rate analysis). Eighty-nine of the screened references were eventually assessed as full-text. Seventy-one[1–71] of these publications were excluded, mostly because they assessed the association between HCC and diabetes (rather than NASH itself), because they used fixed-time outcome measures (eg, a simple retrospective odds ratio on the association between HCC and NAFLD), because of an ill definition of NAFLD, or because of a lack of data to calculate tumor incidence rates. Detailed reasons for exclusion can be found in Supplementary Table 1.

Web of Science n = 11,052

PubMed n = 9308

Embase n = 4576

Central n = 476

All databases combined n = 25,412

After duplicates removed n = 10,254

Web of Science n = 11,052

(TS=(nonalcoholic fatty liver OR nafld OR nbnc OR nafl OR non alcoholic fatty liver disease OR non-alcoholic fatty liver OR non-alcoholic fatty liver disease OR nonalcoholic fatty liver disease OR non-alcoholic steatohepatitis OR nonalcoholic steatohepatitis OR non-alcoholic steato-hepatitis OR non-alcoholic steato hepatitis OR non alcoholic steatohepatitis OR non alcoholic steato-hepatitis OR non alcoholic steato hepatitis OR nonalcoholic steato-hepatitis OR nonalcoholic steato hepatitis OR fatty liver disease OR fatty liver OR non-alcoholic steatosis OR nonalcoholic steatosis OR non alcoholic steatosis OR non viral hepatitis OR non-viral hepatitis OR non b non c OR non-b non-c OR nash OR steato-hepatitis OR steatohepatitis OR liver steatosis OR steatosis OR metabolic syndrome OR liver fat infiltration) AND TS=(liver cell carcinoma OR hepatic carcinoma OR liver cell carcinoma OR hepatic cell carcinoma OR hepatocarcinoma OR hepatocellular carcinoma OR hepatoma OR liver carcinoma OR primary liver carcinoma OR malignant hepatoma OR hcc OR carcinoma of the liver))

PubMed n = 9308

((“Non-alcoholic Fatty Liver Disease"[Mesh]) OR ((fatty) AND liver)) OR nash) OR nonalcoholic steatohepatitis) OR ((nonalcoholic) AND steatohepatitis)) OR ((non-alcoholic) AND steatohepatitis)) OR ((nonalcoholic) AND steatosis)) OR ((non-alcoholic) AND steatosis)) OR nafld) OR ((fatty) AND cirrhosis)) OR ((metabolic syndrome) AND liver)) OR ((metabolic syndrome) AND steatosis)) OR ((metabolic syndrome) AND cirrhosis)) OR diabetes[MeSH Terms]) OR ((diabetes [MeSH Terms]) AND liver)) OR ((diabetes) AND steatosis)) OR ((diabetes) AND steatohepatitis)) OR ((obesity [MeSH Terms]) AND liver cirrhosis[MeSH Terms])) OR ((obesity[MeSH Terms]) AND steatosis)) OR ((obesity [MeSH Terms]) AND steatohepatitis)) OR ((obesity[MeSH Terms]) AND fibrosis)) OR ((non-viral) AND steatosis)) OR ((nonviral) AND steatosis)) OR (((non-viral) AND fatty) AND liver)) OR (((nonviral) AND fatty) AND liver)) OR ((non-viral) AND liver cirrhosis[MeSH Terms])) OR ((nonviral) AND liver cirrhosis[MeSH Terms])) OR (((non-b non-c) AND fatty) AND liver)) OR (((nbnc) AND fatty) AND liver)) OR ((non-b non) AND liver cirrhosis [MeSH Terms])) OR ((nbnc) AND liver cirrhosis[MeSH Terms])) OR ((nbnc) AND steatosis)) OR ((non-b non-c) AND steatosis)) OR ((nbnc) AND steatohepatitis)) OR ((non-b non-c) AND steatohepatitis))) AND ((((((((((((((((((((hepatocellular carcinoma[MeSH Terms]) OR ((neoplasms[MeSH Terms]) AND liver)) OR hcc) OR ((hepatocellular) AND carcinoma)) OR ((cancer) AND liver)) OR ((carcinoma) AND liver)) OR ((hepatic) AND cancer)) OR ((hepatic) AND carcinoma)) OR ((hepatic) AND malignancy)) OR hepatoma) OR ((liver) AND mortality)) OR ((liver) AND outcome)) OR ((liver) AND transplant)) OR ((liver) AND transplantation)) OR ((hepatic) AND transplant)) OR ((hepatic) AND transplantation)) OR ((liver) AND risk)) OR ((liver) AND rate)) OR ((liver) AND incidence)) OR ((liver) AND prevalence)) OR (((liver) AND natural) AND history))) AND ((((((((((((((((((meta-analysis[MeSH Terms]) OR ((systematic) AND review)) OR clinical trial[Publication Type]) OR case-control studies[MeSH Terms]) OR retrospective studies[MeSH Terms]) OR ((case) AND series)) OR ((comparative) AND study)) OR cohort studies[MeSH Terms]) OR cross-sectional studies[MeSH Terms]) OR epidemiology[MeSH Terms]) OR risk) OR rate) OR odds) OR prevalence) OR incidence) OR mortality) OR hazard) OR ((natural) AND history))

Embase n = 4576

('nonalcoholic fatty liver'/de OR nafld:ab,ti OR nbnc:ab,ti OR nafl:ab,ti OR (((’non alcoholic’ OR ’non-alcoholic’ OR ’nonalcoholic’) NEAR/1 (’fatty liver disease’ OR ’fatty liver’ OR ’steatosis’ OR steatohepatitis OR ’steato-hepatitis’ OR ’steato hepatitis’)):ab,ti) OR ’non viral hepatitis’:ab,ti OR ’non-viral hepatitis’:ab,ti OR ’non b non c’:ab,ti OR ’non-b non-c’:ab,ti OR ’fatty liver’:ab,ti OR ’nash’:ab,ti OR ’steato-hepatitis’:ab,ti OR ’steatohepatitis’:ab,ti OR ’liver steatosis’:ab,ti OR ’steatosis’:ab,ti OR ’metabolic syndrome’:ab,ti OR ’liver fat infiltration’:ab,ti) AND (’liver cell carcinoma’/de OR (((’hepatic’ OR ’liver cell’ OR ’hepatic cell’ OR ’hepatocellular’ OR ’liver’) NEXT/1 (carcinoma OR cancer)):ab,ti) OR hepatocarcinoma:ab,ti OR hepatoma:ab,ti OR ’malignant hepatoma’:ab,ti OR ’hcc’:ab,ti OR ’carcinoma of the liver’:ab,ti) NOT [medline]/lim

Central n = 476

(nafld:ab,ti or nbnc:ab,ti or nafl:ab,ti or (('non alcoholic' or 'non-alcoholic' or 'nonalcoholic') near/1 ('fatty liver disease' or 'fatty liver' or 'steatosis' or steatohepatitis or 'steato-hepatitis' or 'steato hepatitis')):ab,ti or 'non viral hepatitis':ab,ti or 'non-viral hepatitis':ab,ti or 'non b non c':ab,ti or 'non-b non-c':ab,ti or 'fatty liver':ab,ti or 'nash':ab,ti or 'steato-hepatitis':ab,ti or 'steato-hepatitis':ab,ti or 'liver steatosis':ab,ti or 'steatosis':ab,ti or 'metabolic syndrome':ab,ti or 'liver fat infiltration':ab,ti) and ((('hepatic' or 'liver cell' or 'hepatic cell' or 'hepatocellular' or 'liver') near/1 (carcinoma or cancer)):ab,ti or hepatocarcinoma:ab,ti or hepatoma:ab,ti or 'malignant hepatoma':ab,ti or 'hcc':ab,ti or 'carcinoma of the liver':ab,ti)

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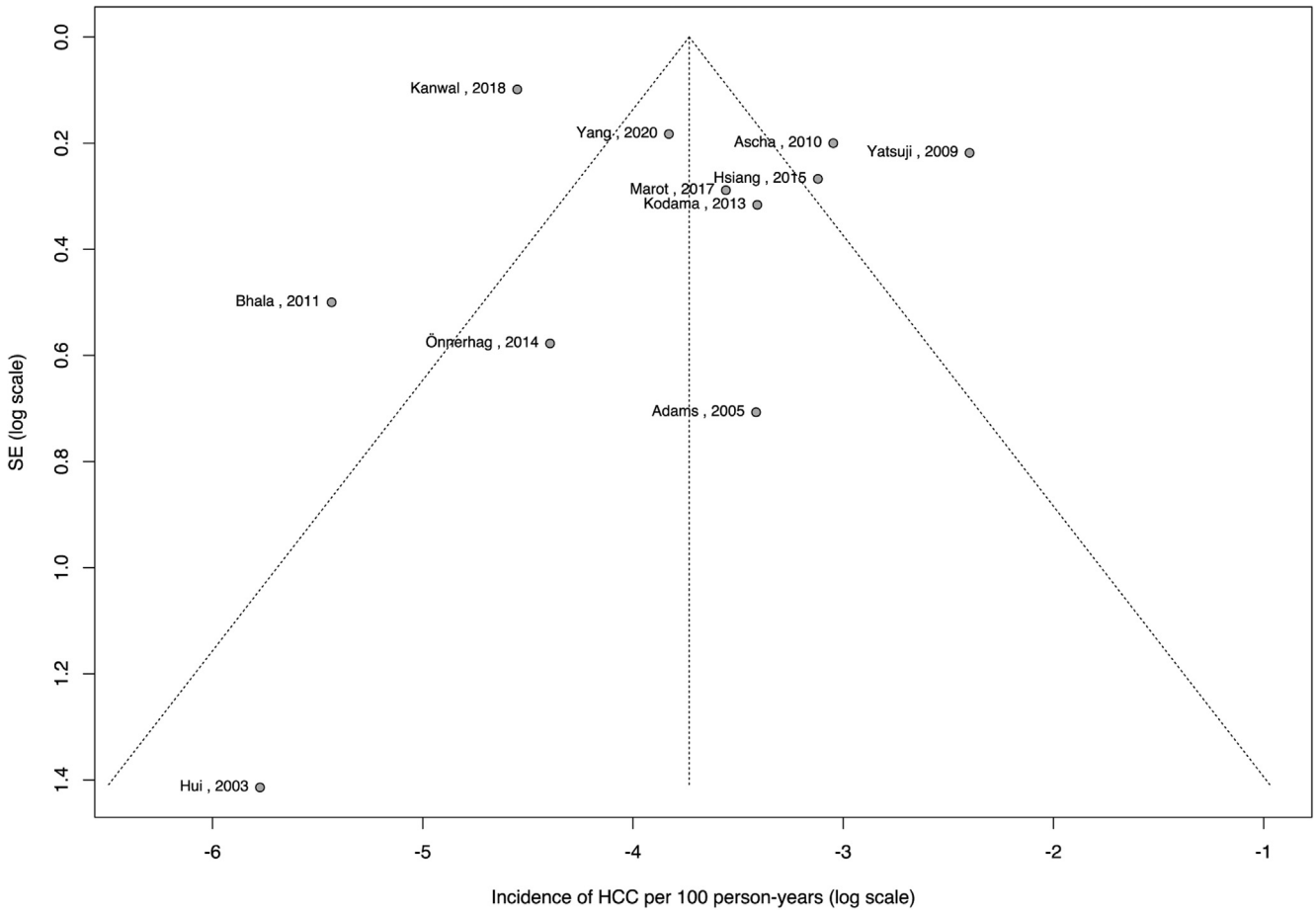


**Supplementary Figure 1.** Funnel plot.

**Supplementary Table 1.** Reason for Excluding 71 Out of the 89 Selected Articles

| First author | Reason for exclusion |
|---|---|
| Abe[1] | Non-B, non-C HCC, cryptogenic cirrhosis |
| Amarapurkar[2] | Inadequate design |
| Anagnostopoulos[3] | Inadequate design |
| Archambeaud[4] | Not clearly NAFLD-related |
| Atchinson[5] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Beste[70] | More recent estimates in the same veterans population are available |
| Borena[6] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Cho[7] | Inadequate design |
| Cotrim[8] | Inadequate design |
| David[9] | Inadequate design, looks at prevalence of given risk factors of HCC in patients with NAFLD |
| Dyson[10] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Ertle[11] | Inadequate design, cross-sectional survey and comparison of patients' characteristics |
| Feng[12] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Guzman[13] | Inadequate design, identification and assessment of three cases |
| Hashimoto[14] | Inadequate design, possible population overlap with other studies |
| Hashizume[15] | Inadequate design, description of selected cases of NAFLD-HCC and NAFLD-cholangiocarcinoma |
| Hernandez-Alejandro[71] | Inadequate design |
| Hucke[16] | Inadequate design, characteristics of patients with HCC in Austria (not particularly NAFLD-oriented) |
| Imura[17] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Jain[18] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Kutsenko[19] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Leung[20] | Inadequate design |
| Leung[21] | Inadequate design, clinical characteristics of 54 patients with NAFLD-HCC |
| Liu[22] | Association between a given genotype and HCC |
| Mair[23] | Not really NAFLD-oriented |
| Marrero[24] | Inadequate design, point prevalence of given etiologies among US patients with NASH |
| Masuzaki[25] | Inadequate design, opinion/review |
| Mittal[26] | More recent estimates in the same veterans population are available |
| Mittal[27] | More recent estimates in the same veterans population are available |
| Mohamad[28] | Inadequate design, comparison of NAFLD-related HCC patients with or without underlying cirrhosis. |
| Mohsen[29] | Inadequate design |
| Mukherjee[30] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Nderitu[31] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Perumpail[32] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Petrick[33] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Piscaglia[34] | Inadequate design, comparison of NAFLD-related and HCV-related HCC patients, looking at tumor morphology and survival |
| Ratziu[35] | Non-B, non-C HCC, cryptogenic cirrhosis |
| Reddy[36] | Inadequate design, evaluates treatment response rather than describing incidence |
| Rodrìguez de Lope[37] | Inadequate design, comparison of patients' characteristics rather than interest in the rate of incidence |

**Supplementary Table 1.** Continued

| First author | Reason for exclusion |
|---|---|
| Schutte[38] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Schutte[39] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Seko[40] | Association between a given genotype and HCC |
| Seko[41] | Association between a given genotype and HCC |
| Stepanova[42] | Inadequate design, looks at survival of patients with NASH or non-inflammatory NAFLD |
| Sun[43] | Inadequate design looks at nonalcoholic cirrhosis as a risk for digestive tract malignancies, but in the group of cirrhosis included HBV-HCV patients. The whole NAC group (non-OH cirrhosis, including viral etiology), used to calculate HCC and other tumors' incidence rates. |
| Takamatsu[44] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Takuma[45] | Inadequate design |
| Tateishi[46] | Inadequate design, comparison of patients' characteristics rather than interest in the rate of incidence |
| Than[47] | Inadequate design |
| Tokushige[48] | Inadequate design |
| Tokushige[49] | Inadequate design |
| Turati[50] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| van Meer[51] | Inadequate design, group aggregation makes it impossible to extract relevant data for the purpose of the current systematic review |
| van Meer[52] | Inadequate design, group aggregation makes it impossible to extract relevant data for the purpose of the current systematic review |
| Weinmann[53] | Inadequate design, compares NAFLD-related HCC with HCC from other etiologies, looking at survival and other outcomes. Does not look at the incidence |
| Weinmann[54] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Welzel[55] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Yang[56] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Yang[57] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Yang[58] | Population overlap with another study (Yang et al, 2020) |
| Yasui[59] | Inadequate design, looks at characteristics of patients with NAFLD-HCC |
| Yoshioka[60] | Full-text should not have been assessed because this is a case report, but quick abstract reading among thousands leads to full-text scrutiny. |
| Younossi[61] | Inadequate design. Assesses proportion of HCC among patients with different types of liver disease. |
| Yu[62] | Metabolic syndrome, diabetes, not clearly NAFLD-related |
| Zen[63] | Inadequate design, wrongfully selected abstract |
| Liu[64] | HCC incidence not reported according to etiology or criteria in present study |
| Sangaramoorthyy[65] | HCC incidence not reported according to etiology or criteria in present study |
| Tobari[66] | HCC incidence not reported according to etiology or criteria in present study |
| Bugianesi[67] | NAFLD not clearly defined |
| Paradis[68] | NAFLD not clearly defined |
| Schulz[69] | NAFLD not clearly defined |

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAC, N-acetylcysteine.

**Supplementary Table 2.** NAFLD Definition, Presence of Simple Steatosis, NASH, and Cirrhosis Among the Included Studies

| First author | Year of publication | NAFLD/NASH definition | Total number of NAFLD (NAFLD, NASH, or both) | Patients with NAFLD non-NASH (%) | Patients with NASH (%) | NAFLD patients with cirrhosis (%) |
|---|---|---|---|---|---|---|
| Hui | 2003 | Histology | 23 | NA | 100 | 100 |
| Adams | 2005 | Histology and/or ultrasound and/or CT scan and/or MRI | 420 | 88.3 | 11.7 | NA |
| Ekstedt | 2006 | NA | 88 | 19.3 | 80.7 | 4.5 |
| Hashimoto | 2009 | Histology | 382 | NA | 100 | 35.8 |
| Yatsuji | 2009 | Histology | 68 | NA | 100 | 100 |
| Ascha | 2010 | Histology or metabolic syndrome without alcohol or viral hepatitis | 195 | 0 | 0 | 100 |
| Bhala | 2011 | Histology | 247 | NA | NA | 52.2 |
| Arase | 2012 | US | 1600 | NA | NA | NA |
| Kawamura | 2012 | US | 6508 | NA | NA | NA |
| Kodama | 2013 | Histology and absence of alcohol or viral hepatitis | 72 | NA | NA | 100 |
| Önnerhag | 2014 | Histology | 36 | 61.1 | 38.9 | 25 |
| Hsiang | 2015 | Histology or transient elastography or radiology | 122 | NA | NA | 100 |
| Kim | 2017 | US | 8721 | NA | NA | NA |
| Lee | 2017 | NA | 18,080 | NA | NA | NA |
| Marot | 2017 | Histology and/or absence of alcohol or viral hepatitis or other cause of liver disease | 78 | NA | NA | 100 |
| Kanwal | 2018 | Laboratory | 296,707 | NA | NA | 0.5 |
| Alexander | 2019 | NA | 136,703 | NA | NA | 0 |
| Yang | 2020 | NA | 354 | 0 | 100 | 100 |

CT, computed tomography; MRI, magnetic resonance imaging; NA, not available; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; US, ultrasound.

**Supplementary Table 3.** Quality of Included Studies

| Study | Barcelona | Geneva | Consensus (quality) |
|---|---|---|---|
| Hui | 1 | 1 | 1 |
| Adams | 0 | 0 | 0 |
| Ekstedt | 1 | 0 | 1 |
| Hashimoto | 1 | 1 | 1 |
| Yatsuji | 1 | 1 | 1 |
| Ascha | 0 | 0 | 0 |
| Bhala | 0 | 0 | 0 |
| Arase | 2 | 2 | 2 |
| Kawamura | 1 | 1 | 1 |
| Kodama | 0 | 1 | 1 |
| Önnerhag | 0 | 0 | 0 |
| Hsiang | 0 | 1 | 1 |
| Kim | 1 | 1 | 1 |
| Lee | 1 | 1 | 1 |
| Marot | 1 | 1 | 1 |
| Kanwal | 1 | 1 | 1 |
| Alexander | 0 | 0 | 0 |
| Yang | 0 | 0 | 0 |

NOTE. On the basis of the National Institutes of Health Study Quality Assessment Tool, studies were given 0, 1, or 2 points, corresponding to low, moderate, and high risk of bias, respectively.

**Supplementary Table 5.** Output of Meta-regression Analyses

| Variable[a] | Coefficient *P* value | $I^2$ | $\tau^2$ | *P* value for heterogeneity |
|---|---|---|---|---|
| Duration of inclusion (*y*) | .6 | 92% | 0.68 | <.001 |
| Age (*y*) | .049 | 87% | 0.45 | <.001 |
| % of males | .3 | 87% | 0.6 | <.001 |
| % of diabetics | .12 | 85% | 0.51 | <.001 |
| Year of publication (≤2010 vs >2010) | .07 | 86% | 0.42 | <.001 |
| MELD score | .2 | 90% | 0.59 | <.001 |
| ALT (*IU/L*) | .18 | 88% | 1.15 | <.001 |
| AST (*IU/L*) | .4 | 86% | 1.37 | <.001 |
| Platelet count ($10^9$/*L*) | .3 | 90% | 0.74 | <.001 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease.
[a]All meta-regressions are subject to data availability. Some values have been transformed from median to unify average values between studies.

**Supplementary Table 4.** Sensitivity Analyses

| | No. of studies | Pooled incidence of HCC in NAFLD in cirrhotic patients per 100 person-years (95% CI) | $I^2$ | $\tau^2$ | *P* value for heterogeneity |
|---|---|---|---|---|---|
| NAFLD diagnostic tool[a] | | | | | |
| Combination | 5 | 3.96 (3.09–5.06) | 0% | 0 | .61 |
| Lab test | 1 | 1.06 (0.87–1.28) | — | — | — |
| Histology | 4 | 1.36 (0.28–6.60) | 93% | 2.11 | <.01 |
| Epidemiologic design | | | | | |
| Retrospective | 6 | 2.72 (1.62–4.58) | 93% | 0.34 | <.01 |
| Prospective | 5 | 1.68 (0.50–5.62) | 91% | 1.53 | <.01 |
| Location | | | | | |
| Asia (Japan) | 2 | 5.82 (2.09–15.1) | 86% | 0.44 | <.01 |
| USA | 4 | 2.31 (1.13–4.72) | 94% | 0.44 | <.01 |
| Others | 5 | 1.50 (0.57–3.93) | 81% | 0.88 | <.01 |
| Quality | | | | | |
| Good | 4 | 2.75 (1.54–4.91) | 72% | 0.21 | <.01 |
| Fair | 7 | 2.17 (0.95–4.94) | 95% | 1.03 | <.01 |

HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease.
[a]Yang 2020, not available.

**Supplementary Table 6.** Leave-One-Out Analysis

| Omitted study | Pooled effect (95% CI) | $\tau^2$ | $I^2$ |
|---|---|---|---|
| Hui, 2003 | 2.54 (1.49–4.33) | 0.62 | 93.2% |
| Adams, 2005 | 2.32 (1.31–4.13) | 0.70 | 93.3% |
| Yatsuji, 2009 | 2.08 (1.27–3.40) | 0.46 | 89.0% |
| Ascha, 2010 | 2.19 (1.23–3.91) | 0.68 | 92.1% |
| Bhala, 2011 | 2.84 (1.77–4.56) | 0.43 | 92.8% |
| Kodama, 2013 | 2.29 (1.26–4.14) | 0.73 | 93.2% |
| Önnerhag, 2014 | 2.52 (1.43–4.44) | 0.67 | 93.2% |
| Hsiang, 2015 | 2.22 (1.24–3.97) | 0.70 | 92.8% |
| Marot, 2017 | 2.32 (1.28–4.22) | 0.74 | 93.2% |
| Kanwal, 2018 | 2.68 (1.55–4.63) | 0.59 | 83.0% |
| Yang, 2020 | 2.39 (1.31–4.37) | 0.74 | 93.3% |
| Pooled estimate | 2.39 (1.40–4.08) | 0.64 | 93% |

CI, confidence interval.