

Hepatic Resection for Hepatocellular Carcinoma in Nonalcoholic Fatty Liver Disease

A Systematic Review and Meta-Analysis of 7226 Patients

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Objective: To systematically review and compare the overall (OS) and disease-free (DFS) survival after hepatic resections for hepatocellular carcinoma (HCC) of patients with nonalcoholic fatty liver disease (NAFLD) versus other risk factors.

Background: Different clinical and tumor characteristics are associated with HCC in the setting of NAFLD in comparison to other risk factors. It is still unclear whether these differences impact patient survival after radical hepatectomies.

Methods: Randomized controlled trials and observational studies published in the English literature between July 1980 and June 2020 were searched using multiple databases. Patients' baseline characteristics and the hazard ratios (HRs) of the OS and DFS were extracted and meta-analyses were performed.

Results: Fifteen retrospective cohort studies with a total of 7226 patients were included. Among them, 1412 patients (19.5%) had NAFLD and 5814 (80.4%) had other risk factors (eg, viral hepatitis B or C, alcoholic cirrhosis, or cryptogenic cirrhosis). Summary statistics showed that patients with NAFLD had better DFS (HR = 0.81; 95% CI: 0.70–0.94; $P = 0.006$) and OS (HR = 0.78; 95% CI: 0.67–0.90; $P = 0.001$) than the control group. Subgroups analyses also indicated that the OS favored NAFLD patients versus patients with viral hepatitis B or C (HR = 0.80; 95% CI: 0.67–0.96; $P = 0.017$) or alcoholic and cryptogenic cirrhosis (HR = 0.68; 95% CI: 0.47–1.0; $P = 0.05$).

Conclusion: After hepatic resections for HCC, NAFLD patients have better DFS and OS than patients with other risk factors. Subgroup analysis and meta-regression suggested that the survival advantage of NAFLD patients was more pronounced in studies published after 2015 and from Asian centers.

Keywords: meta-analysis, meta-regression, systematic review, hepatoma, hepatocellular carcinoma, hepatic resection, nonalcoholic steatohepatitis, nonalcoholic fatty liver disease, overall survival, disease-free survival, viral hepatitis B, viral hepatitis C, cryptogenic cirrhosis, alcoholic cirrhosis

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver and the fifth most frequent malignancy worldwide.¹ Surgery, in the form of liver transplantation or hepatic resection, provides the longest survival.^{2–4} Liver transplantation has the best cure rate,^{5–7} however, resection is the most common surgical therapy as liver transplantation is limited by the number of donors and, in some countries, by insufficient resources.^{5–7}

Worldwide, the highest incidence of HCC is found in South-East Asia and sub-Saharan Africa while the lowest is found in North America and Northern Europe.⁸ These geographical differences are due to distinct risk factors. While hepatitis B virus (HBV) is the primary cause of HCC in Asia and Africa,^{9,10} viral hepatitis C (HCV), alcoholic cirrhosis, and nonalcoholic fatty liver disease (NAFLD) are the most common risk factors in Europe and the United States.¹¹

Over the last few decades, the incidence of HCC from viral hepatitis has decreased due to the introduction of vaccination programs for hepatitis B¹² and antiviral drugs for HCV.¹³ The opposite trend, however, is seen for NAFLD¹⁴ not only in Western countries where obesity is widespread but also in Africa, the Middle East, and Asia.^{15–18} The reasons why the prevalence of NAFLD is on the rise globally are still unclear, yet there is growing evidence that there are oncological and clinical differences between HCC in the settings of NAFLD versus other risk factors. For instance, patients with NAFLD have

an upregulation of STAT-1 and STAT-3, 2 proteins linked to hepatocarcinogenesis in the absence of cirrhosis.^{19,20} Also, compared to tumors from other risk factors, HCC in the settings of NAFLD has different gene regulatory networks²¹ and nucleotide polymorphisms.²² Whether these differences impact the survival after hepatic resections with curative intent remains uncertain. While some studies have suggested that patients with NAFLD have worse outcomes,^{23–26} others have reported opposite finding^{27–37} even though patients with NAFLD are usually older and with more comorbidities.^{19,38,39}

To better understand the outcomes of NAFLD patients compared to patients with other risk factors, we performed a systematic review and a meta-analysis to test the null hypothesis that there are no significant differences in the overall survival (OS) and disease-free survival (DFS) between the 2 groups after radical resections for HCC. Our secondary aim was to assess if the results of the meta-analyses were dependent on specific effect modifiers such as the presence of cirrhosis, etiology of liver disease, geography, and year of publication.

MATERIAL AND METHODS

This study was structured using the Population, Intervention, Comparison, Outcome (PICO) template. Adult patients (18 years or older) represented the study population irrespective of ethnicity or risk factors for HCC. For intervention, we selected hepatic resections performed with curative intent. Patients who had synchronous locoregional therapies such as radiofrequency or microwave ablations at the time of hepatic resections were excluded. The surgical techniques (eg, open surgery, laparoscopic surgery, or hybrid surgery), and the extent of resection (eg, lobectomy, segmentectomy, trisegmentectomy, or nonanatomical resections) were not factors included in the analysis. All comparisons were made between patients with NAFLD versus other risk factors for HCC. The primary outcome measure was the OS, while the secondary outcome was the DFS.

The PRISMA (preferred reporting items for systematic reviews and meta-analyses)⁴⁰ and MOOSE (meta-analysis of observational studies in epidemiology)⁴¹ guidelines were used for the conduct and reporting of this study. (Appendices S1 and S2, Supplementary Table 1, <http://links.lww.com/AOSO/A37>, and Supplementary Table 2, <http://links.lww.com/AOSO/A37>.)

Data Sources and Searches

A systematic review of the English literature was completed according to a protocol that outlined the primary and secondary objectives, the inclusion and exclusion criteria of the studies, the type of data to be collected, and the statistical analysis to be performed. The protocol was registered with the PROSPERO database at www.crd.york.ac.uk/prospere, registration number CRD 207395.

The PubMed/MEDLINE, EMBASE, Scopus, Google Scholar, the Cochrane Library, Web of Science, ClinicalTrials.gov, International Clinical Trials Registry Platform, Networked Digital Library of Theses and Dissertations, and Dissertations and Theses Global databases were searched to identify studies published between July 1, 1980, and June 30, 2020. The initial date restriction for the search of the literature was based on the fact that NAFLD was described for the first time in July 1980.⁴²

Since all studies on NAFLD patients occurred after 1980, we searched only databases in the English language as it had already become the international language of choice for scientific publications.

Two health science librarians (C.W. and M.L.K.) developed and executed the search strategy. Searches were limited to studies on humans, published in the English language using terms

and keywords. The subject explosion was used for scientific terms.

Terms and keywords used for the search referred to HCC, hepatoma, liver neoplasm, nonalcoholic steatohepatitis (NASH), NAFLD, surgery, and survival. More specifically, the terms and keywords to identify suitable studies included the following terminology and Boolean logic: (hepatocellular carcinoma OR liver neoplasm OR hepatoma) AND (non-fatty liver disease OR nonalcoholic steatohepatitis) AND (surgery OR resection OR lobectomy OR segmentectomy OR wedge resection OR anatomical resection OR non-anatomical resection) AND (overall survival or disease-free survival or outcomes).

Electronic searches were also complemented by hand-searching of the reference list of identified articles and bibliographies of relevant books and review articles. For studies reporting the outcomes of several treatment groups, each group was assessed for eligibility.

Study Selection

The titles and the abstracts of the retrieved articles were stored using the web-based software DistillerSR, (Evidence Partners, Ottawa, Canada). Two independent investigators (M.M. and P.B.S.) screened the titles to assess if they were relevant for this study. When the content of the titles was not sufficiently informative, the respective abstracts and articles were fully appraised.

Randomized controlled trials, quasi-randomized controlled studies, case-control, and cohort studies were eligible. Studies were excluded if they were duplicate publications, if hepatic resections were performed on patients with mixed hepatocellular-cholangiocarcinomas or fibrolamellar carcinomas, if patients had previous liver transplants, or if they underwent hepatic resections with synchronous combined locoregional therapies such as ablations.

When the same institution or the same group of investigators published data originating from cohorts of patients at different time intervals, we included only the articles with the largest population or the articles with the highest quality.

Studies that did not report sufficient data on patient survival after hepatic resections were also excluded.

Data Extraction

All variables used for this meta-analysis were abstracted by 2 independent investigators (M.M. and P.B.S.). Pertinent data were recorded on standardized preprinted forms developed during the writing of the research protocol. If discrepancies of the data collected by the 2 reviewers (M.M. and P.B.S.) were identified, a third investigator (C.K.) was consulted for reconciliation.

The variables collected for each study were the name of the primary author, the year of publication, the country where patients were enrolled, the type of study design categorized into randomized controlled study, quasi-randomized controlled study and observational study, the year of initiation of the study, the year of completion of the study, the total number of patients enrolled, the number of patients with NAFLD and the number of patients with other types of liver disease, the type of chronic liver disease affecting patients in the control group, the mean or median age of the study population, the mean or median serum level of alpha-fetoprotein (AFP), the percentage of patients with cirrhosis, and the median size or the pTNM stage of the tumors.

The diagnosis of cirrhosis was based on the pathological analysis of the surgical specimens reported in the original studies included in this meta-analysis.

Assessment of Bias

Two independent investigators (P.B.S. and M.M.) assessed the quality of the articles. In the case of discrepancies, a third

researcher (C.K.) was consulted. Since no randomized controlled studies were identified by the literature search, the Newcastle-Ottawa Assessment Scale (NOS)²⁰ was used to measure the quality of the articles.

The NOS is a validated instrument^{43,44} designed to assess the quality of nonrandomized studies for meta-analyses.²⁰ It contains 8 multiple-choice questions that are related to the selection of patients, their comparability, and their outcomes (Supplementary Table 3, <http://links.lww.com/AOSO/A37>).

In the NOS, 9 stars represent the highest level of quality. Studies with 7 or more stars are categorized as good quality, 5 to 6 stars indicate fair quality, and 4 or fewer stars indicate poor quality. Stars are allocated as follows: up to 4 stars for patient selection, up to 2 stars for comparability, and up to 3 stars for exposure/outcomes.

Publication bias was evaluated using funnel plots quantified by Egger regression analysis.⁴⁵

Endpoints

The primary and secondary aims of this study were the OS and the DFS of NAFLD patients versus patients with other risk factors for HCC. Within the control group, risk factors for HCC were categorized into viral hepatitis (B, C, or other), alcoholic cirrhosis, cryptogenic cirrhosis, and unspecified. The OS was defined as the time between the date of hepatic resection and the date of death from any cause. The DFS was defined as the time between the date of hepatic resection and the date of diagnosis of recurrent HCC by radiological tests, rising levels of serum tumor markers, physical examination, or the combination of all 3 modalities.

Summary Statistics

The hazard ratios (HRs) with corresponding 95% confidence intervals (95% CIs) were used as measures of treatment effects. When studies reported both the crude and the adjusted HRs (aHR), the aHR was preferred.

For studies where the HR was not available, an indirect estimate of the HRs with respective 95% CIs was obtained using Parmar's methodology.⁴⁶ Parmar's methodology allows the calculation of the HR using data obtained from Kaplan-Meier survival curves or using the actuarial percentages of surviving patients at specific time intervals. Digitizelt, a software designed to extract data from scientific graphics, was used to compute the percentages of surviving patients for the indirect calculation of the HR. The percentages of patients who survived at different time intervals were subsequently entered in an open-access Microsoft Excel spreadsheet calculator⁴⁶ developed to compute the HR and 95% CI by the cooperation of the Meta-Analysis Group, MRC Clinical Trials Unit, London, UK, School of Public Health, Sydney, Australia, and MRC Clinical Trial Unit, London, UK.⁴⁷ The HR calculator used for this study is publicly accessible at the Uniform Resource Locator: <http://www.biomedcentral.com/content/supplementary/1745-6215-8-16-S1.xls>.

Data Synthesis

The random-effect model⁴⁸ was used for all the summary statistics and meta-regressions.⁴⁹ For meta-regressions, the year of publication and the proportion of NAFLD patients affected by cirrhosis were used as independent variables (potential effect modifiers). The heterogeneity among studies was assessed using the I^2 statistics.⁵⁰ I^2 is an estimate of the proportion of variability due to between-study heterogeneity rather than by sampling errors.⁵¹ I^2 values of 25%, 50%, and 75% were considered thresholds of a low, moderate, and high degree of heterogeneity, respectively.⁵⁰

All statistical analyses were performed using Comprehensive Meta-Analysis (CMA) Version 3 (Biostat Inc.) and 2-tailed P values of 0.05 were considered statistically significant.

RESULTS

The initial electronic search yielded 179,908 articles. During the first screening, 145,603 articles were excluded based on the content of their titles. The remaining 33,980 studies underwent a second screening, and 10,723 articles were excluded because of duplicate publications and 23,092 articles because they were not relevant for our study.

A total of 165 articles were fully appraised and their references were hand-searched. No additional studies were found by hand search. After reviewing the full content of 165 articles that passed the second screening, we excluded 150 as they did not meet all the inclusion criteria. Inter-rater reliability for the exclusion and inclusion of the studies used for this meta-analysis was 100%, and the final number of articles that were included was 15. The flowchart summarizing the different stages of the systematic review of the literature, the number of retrieved studies, and the reasons for their exclusion are reported in Figure 1.

Study Characteristics

The main characteristics of the articles used for this meta-analysis are reported in Supplementary Table 4, <http://links.lww.com/AOSO/A37>. Patients were enrolled over 25 years (from 1990 to 2015), 11 studies (73.3%) were from Asia, 3 (20%) were from Europe, and 1 (6.6%) was from the United States. All studies were retrospective cohort studies of good quality. The summary of the quality metrics of the studies based on the NOS is summarized in Appendix S4, Supplementary Table 5, <http://links.lww.com/AOSO/A37>. Interrater reliability for the quality of the studies was 86%. The funnel plot of the log of the HR (x-axis) over the standard error (y-axis)⁴⁵ had a symmetric distribution suggesting a low-risk of publication bias (see Appendix S5, Supplementary Figure 1S, <http://links.lww.com/AOSO/A37>).

Patient and Tumor Characteristics

Baseline characteristics of the study population are reported in Supplementary Table 6, <http://links.lww.com/AOSO/A37>. The total number of patients was 7226 with a median/mean age ranging between 51 and 72 years, 1412 (19.5%) patients had NAFLD, and 5814 (80.4%) patients had other risk factors for HCC. The minimum follow-up was 24 months, while the longest was 87 months. The prevalence of cirrhosis ranged between 10.5% and 75% for patients with NAFLD, and between 19.1% and 93% for patients within the control group.

Disease-Free Survival

Data on the DFS was available in 12 studies. The 5-year DFS ranged from 24.4% to 66% for NAFLD patients compared to 17.4% to 46.9% for patients within the control group (see Appendix S6, Supplementary Table 7, <http://links.lww.com/AOSO/A37>). The summary statistics from the data obtained from all 12 studies favored NAFLD patients (pooled HR = 0.81; 95% CI = 0.70–0.94; $P = 0.006$; $I^2 = 55.1%$) (Fig. 2A). Rosenthal's⁵² Fail-Safe N analysis estimated that 87 additional studies would be necessary to nullify the difference in DFS between NAFLD patients and the control group.

Subgroup analyses showed no differences in DFS between NAFLD patients and patients with viral hepatitis (B or C) (HR = 0.83; 95% CI: 0.67–1.04; $P = 0.12$; $I^2 = 66.7%$) or patients with other types of nonviral liver diseases (alcoholic or cryptogenic cirrhosis) (HR = 0.81; 95% CI: 0.57–1.13; $P = 0.22$; $I^2 = 25.3%$) (Fig. 2B).

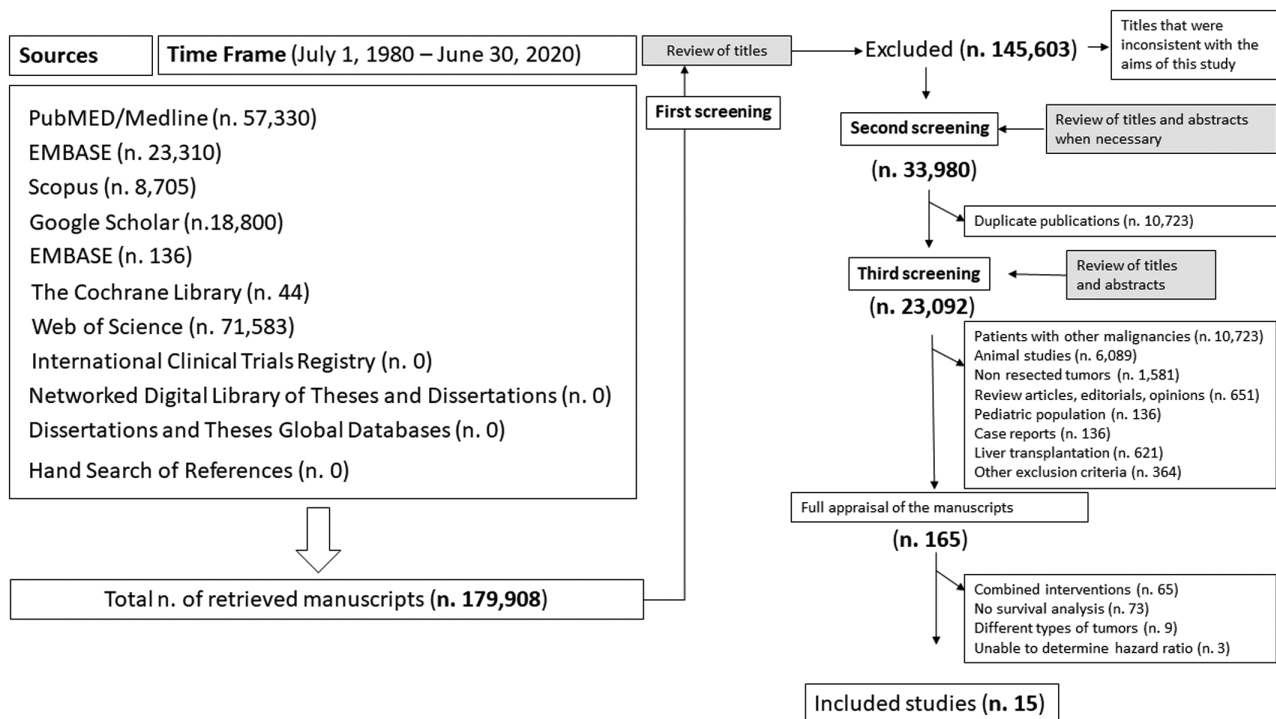


FIGURE 1. Flowchart of the systematic review of the literature throughout different phases. The literature search was performed from July 1, 1980, to June 30, 2020. PubMed/Medline, EMBASE, Scopus, Google Scholar, EMBASE, The Cochrane Library, Web of Science, International Clinical Trials Registry, Network Digital Library of Theses and Dissertations, Dissertations and Theses Global Databases were searched in addition to hand search of references of pertinent articles or books. Initially, a total of 179,908 titles were retrieved. During the first screening, 145,603 articles were excluded as their titles revealed that the respective articles did not fulfill the inclusion criteria. During the second screening, a total of 10,723 articles were excluded because found to be duplicate publications. By the third screening, 23,092 studies were excluded, and the remaining 165 articles were fully appraised. A total of 150 studies were excluded as they did not report postoperative patient survival ($n = 73$), they included patients undergoing multiple interventions ($n = 65$), they included patients with tumors that were not hepatocellular carcinomas ($n = 9$), or the hazard ratios were not reported or there was not enough data to estimate the hazard ratios ($n = 3$). Overall, the total number of studies that were included in this meta-analysis was 15.

Overall Survival

Data on the OS was available in 14 studies. For NAFLD patients, the 5-year OS ranged from 28.1% to 91.1% compared to 21.2% to 79.2% for the control group (see Appendix S7, Supplementary Table 8, <http://links.lww.com/AOSO/A37>). The summary statistics from the data obtained from all 14 studies favored NAFLD patients (pooled HR = 0.78; 95% CI: 0.67–0.90; $P = 0.001$; $I^2 = 87.9\%$) (Fig. 3A).

Rosenthal's ⁽⁵²⁾ Fail-Safe N analysis estimated that a total of 227 additional studies would be necessary to nullify the difference of the OS between NAFLD patients and the control group.

Subgroup analysis showed that patients with NAFLD had a better OS in comparison to patients with viral hepatitis (B or C) (HR = 0.80; 95% CI: 0.67–0.96; $P = 0.01$; $I^2 = 93.1\%$) or nonviral liver diseases (alcoholic or cryptogenic cirrhosis) (HR = 0.68; 95% CI: 0.47–0.99; $P = 0.05$; $I^2 = 12.3\%$) (Fig. 3B).

Meta-Regressions and Subgroup Analyses

We hypothesized that improvement in patient selection, surgical techniques, and perioperative care occurring over the study period might have contributed to the heterogeneity of the data of this meta-analysis. To test our hypothesis, we performed a meta-regression and sensitivity analysis using the year of publication as an independent variable. The meta-regression showed that there was a statistically significant relationship between the log of the HR and the year of publication indicating that the difference in the OS between NAFLD and the control group increased over time (Fig. 4A).

Subgroup analysis was performed using the year 2015 as discriminant to separate studies into 2 groups with a balanced distribution of the number of articles. For studies published before 2015, we found no significant difference in the OS between NAFLD patients and the control group (HR = 0.93; 95% CI: 0.73–1.19; $P = 0.58$; $I^2 = 56.1\%$). On the other hand, when studies published after 2015 were included, the pooled HR for the OS favored NAFLD patients (HR = 0.67; 95% CI: 0.54–0.83; $P = 0.001$; $I^2 = 93.4\%$) (Fig. 4B).

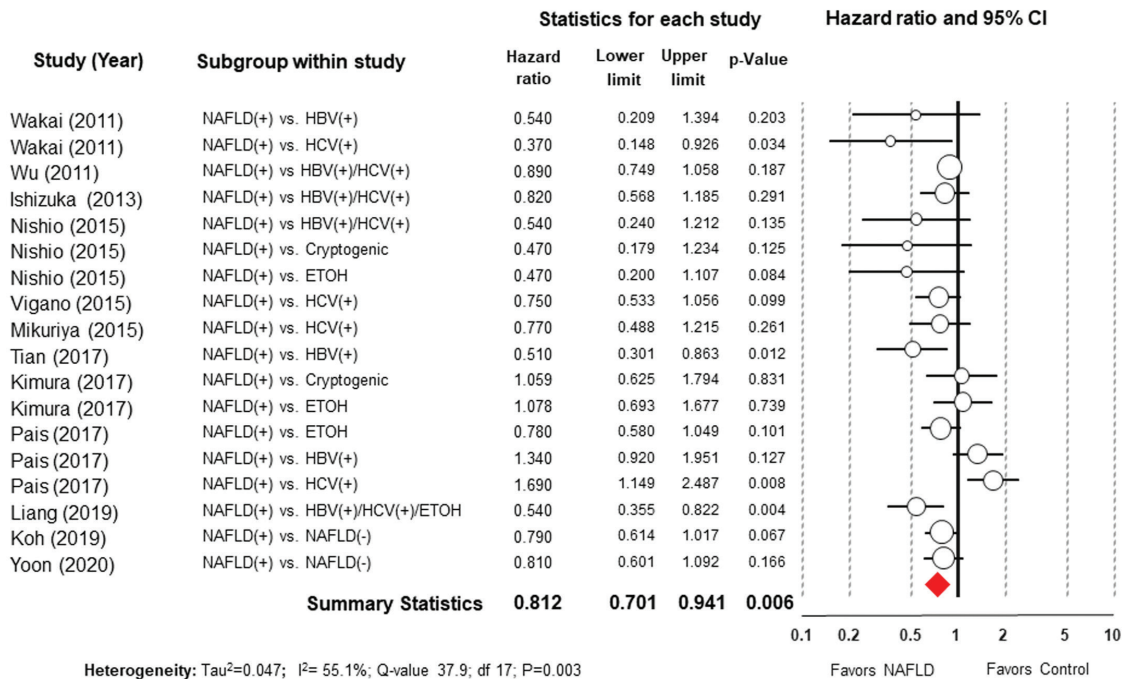
Cirrhosis is a well-known factor affecting postoperative survival after hepatic resections. Therefore, a meta-regression analysis was performed using the prevalence of cirrhosis as a continuous independent variable. Contrary to our hypothesis, we found no statistically significant associations between the HR for DFS and OS and the prevalence of cirrhosis. The summary of the results of meta-regression analysis for DFS and OS are reported in Appendix S8, Supplementary Table 9, <http://links.lww.com/AOSO/A37>.

Subgroup analyses were also performed to determine if the results were influenced by the geographical location where the studies had been performed. The HR for DFS favored NAFLD in Asia (HR = 0.73; 95% CI: 0.62–0.87; $P < 0.001$; $I^2 = 25.2$) while there was no significant difference between the 2 groups for studies performed in Western countries (HR = 1.04; 95% CI: 0.80–1.35; $P = 0.74$; $I^2 = 79.7$) (Fig. 5A).

Similarly, the HR for OS favored NAFLD in Asia (HR = 0.74; 95% CI: 0.61–0.90; $P = 0.003$; $I^2 = 57.9$), while there was no significant difference between the 2 groups in studies performed in Europe or the United States (HR = 0.85; 95% CI: 0.65–1.12; $P = 0.26$; $I^2 = 96.0$) (Fig. 5B).

A

Disease-free Survival



B

Disease-free Survival: Subgroup Analysis Etiology of Liver Disease

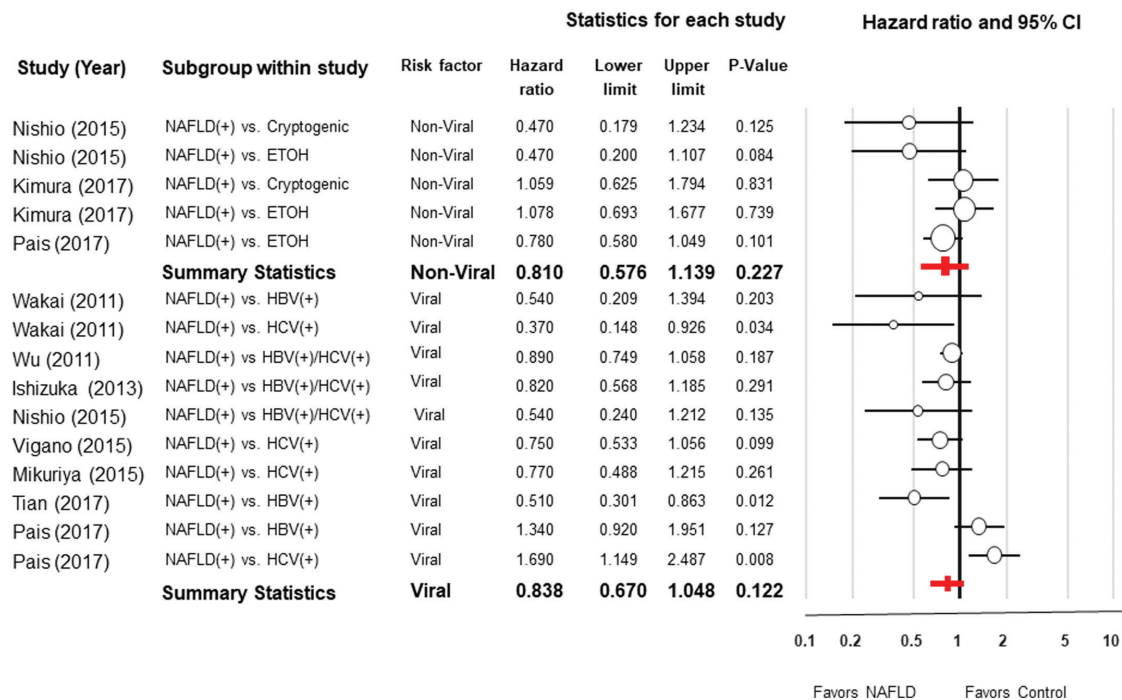


FIGURE 2. Panel A, Forest plot of meta-analysis with random effect model of the disease-free survival (DFS) of patients with nonalcoholic fatty liver disease (NAFLD) after hepatic resection for hepatocellular carcinoma compared to patients with other risk factors. Panel B, Subgroup analysis comparing NAFLD patients with patients with non-viral risk factors (alcoholic or cryptogenic cirrhosis) and with viral hepatitis (B or C).

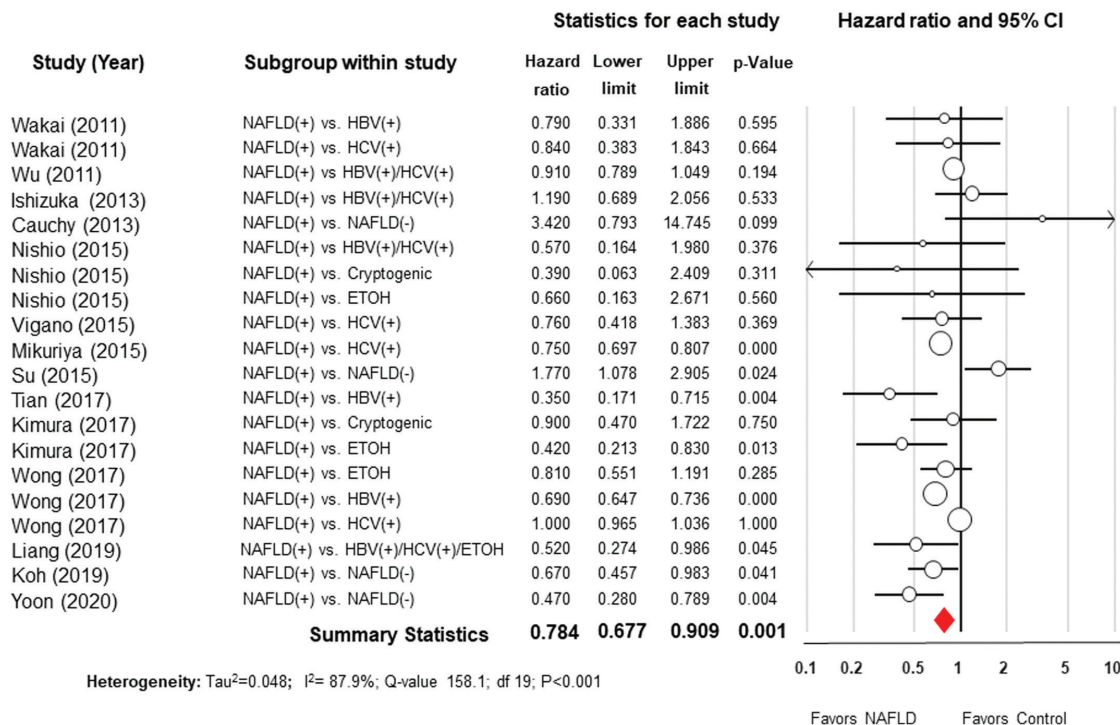
DISCUSSION

Four decades have passed since the term NAFLD was introduced by Ludwig et al⁴² to describe the histological findings consistent with abnormal deposits of fat in the hepatocytes of patients without a history of alcohol abuse. Since then, NAFLD

has become one of the most prevalent liver diseases and a leading cause of HCC worldwide.

The epidemic of NAFLD remains a topic of intense research; however, several important aspects of this condition remain unclear. From the surgical point of view, one of the unanswered

A Overall Survival



B Overall Survival: Subgroup Analysis Etiology of Liver Disease

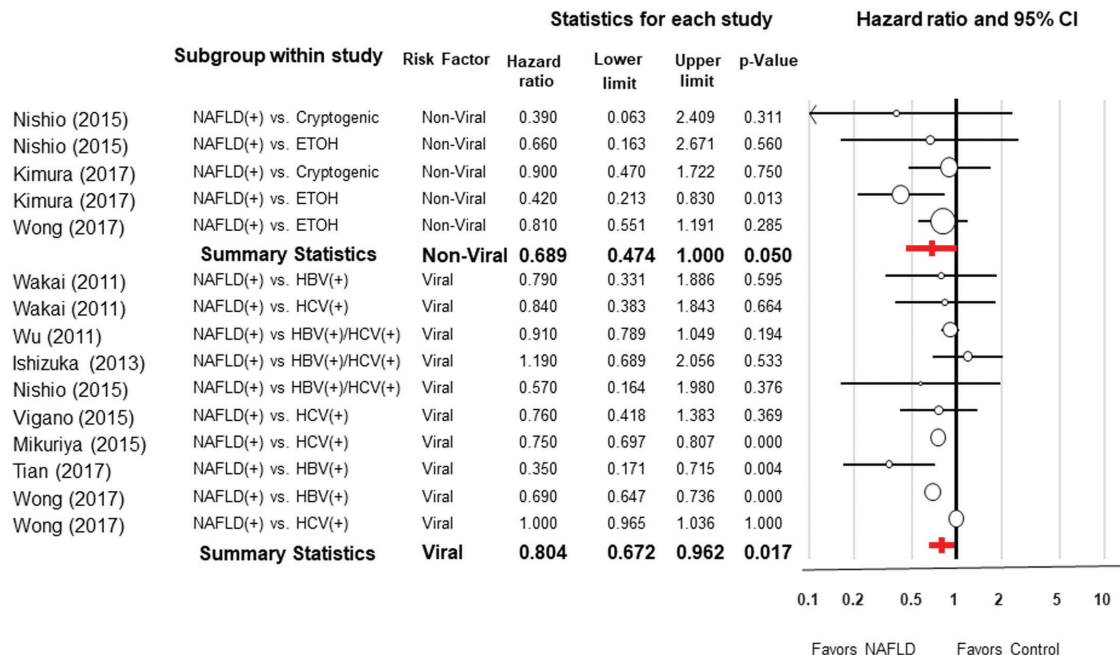
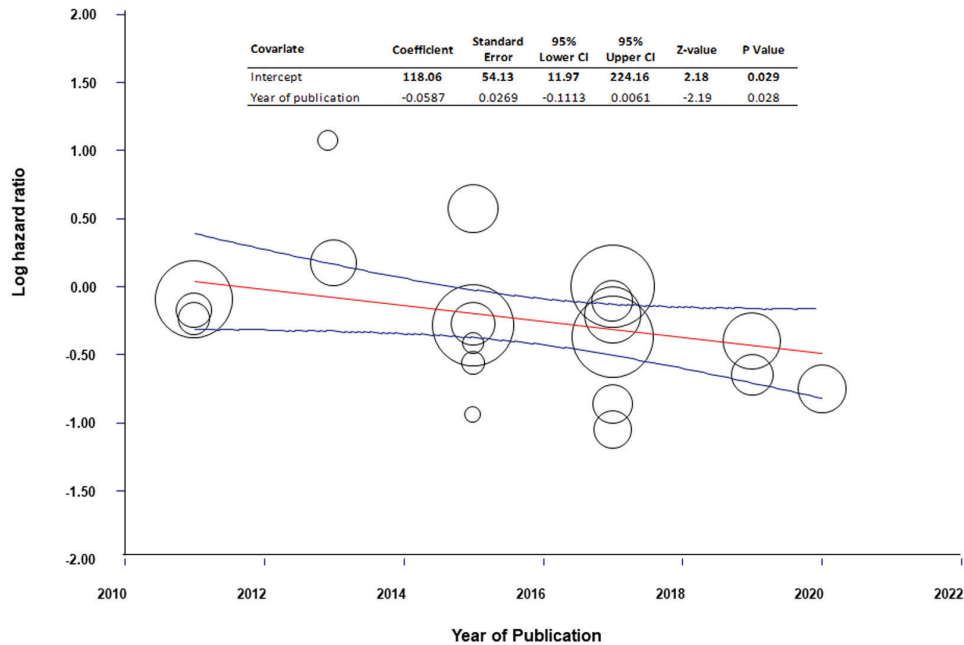


FIGURE 3. Panel A, Forest plot of meta-analysis with random effect model of the overall survival (OS) of patients with nonalcoholic fatty liver disease (NAFLD) after hepatic resection for hepatocellular carcinoma compared to patients with other risk factors. Panel B, Subgroup analysis comparing NAFLD patients with patients with nonviral risk factors (alcoholic or cryptogenic cirrhosis) and in the setting of viral hepatitis (B or C).

questions is whether the survival of NAFLD patients undergoing hepatic resection for HCC is comparable to the survival of patients with other types of chronic liver diseases. While several groups have reported that NAFLD patients have better outcomes,^{28,30} others have found opposite results.^{53,54}

To address this controversial issue, we performed a systematic review and a meta-analysis using data from 15 observational studies that compared the survival of patients treated with radical hepatic resections for HCC in the setting of NAFLD versus patients with viral or nonviral diseases. Since

A
Overall Survival: Meta-Regression of Log Hazard Ratio on Year of Publication



B
Overall Survival: Subgroup Analysis Year of Publication

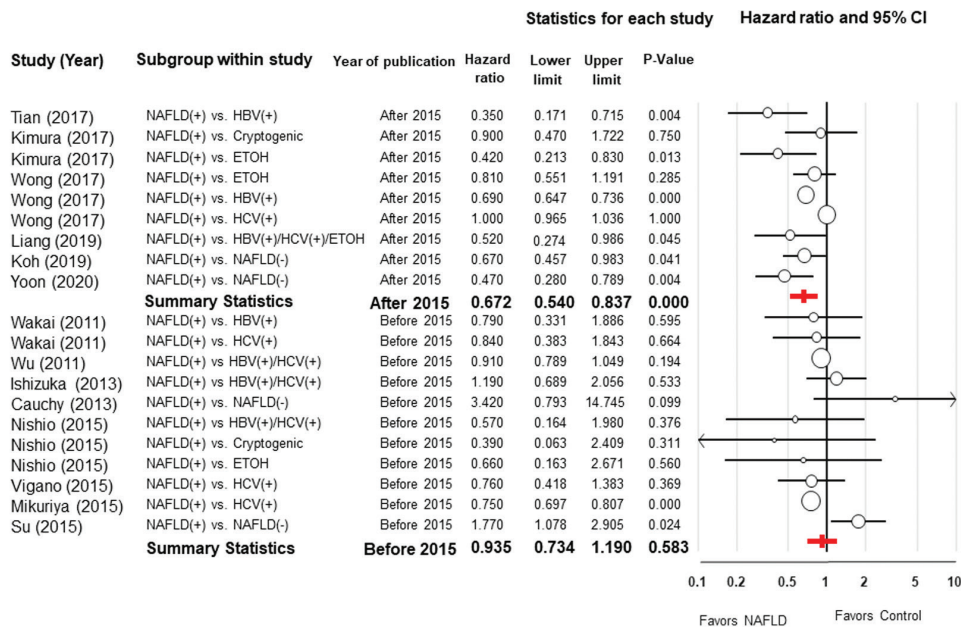
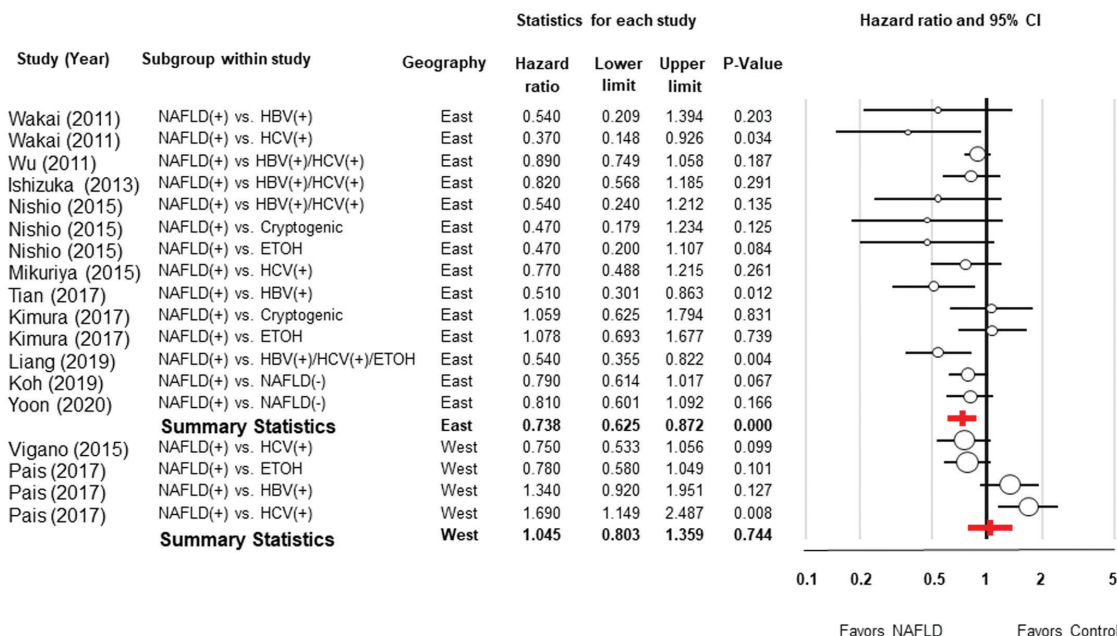


FIGURE 4. Panel A, Univariate meta-regression showing the effects of the year of publication on the log of the hazard ratio (HR). Compared to the control group, the overall survival (OS) advantage of patients with nonalcoholic fatty liver disease (NAFLD) increased over time ($P = 0.02$). Each circle represents a study, and the area of each circle is proportional to the relative weight of the respective study. The central line represents the fitted regression line with respective 95% confidence intervals. Panel B, Forest plot for the sensitivity analysis assessing the effects of the year of publication on the OS of NAFLD patients compared to patients with other risk factors. Studies published after 2015 are reported on the upper part of the forest plot while studies published before 2015 are reported on the lower part of the forest plot.

our primary aim was to characterize the effects of surgery, we did not include studies where patients underwent combined treatments such as hepatic resections and simultaneous ablation therapies. To the best of our knowledge, this is the first meta-analysis to test the null hypothesis that there are no differences in the DFS and OS between these 2 groups of patients.

The main finding of this study was that the HR for the DFS and OS of NAFLD patients was significantly lower than the HR of patients with other risk factors. Sensitivity analysis also indicated that the DFS and the OS were superior for NAFLD patients irrespective of the type of liver disease affecting the control group.

A Disease-free Survival: Subgroup Analysis Based on Geography



B Overall Survival: Subgroup Analysis Based on Geography

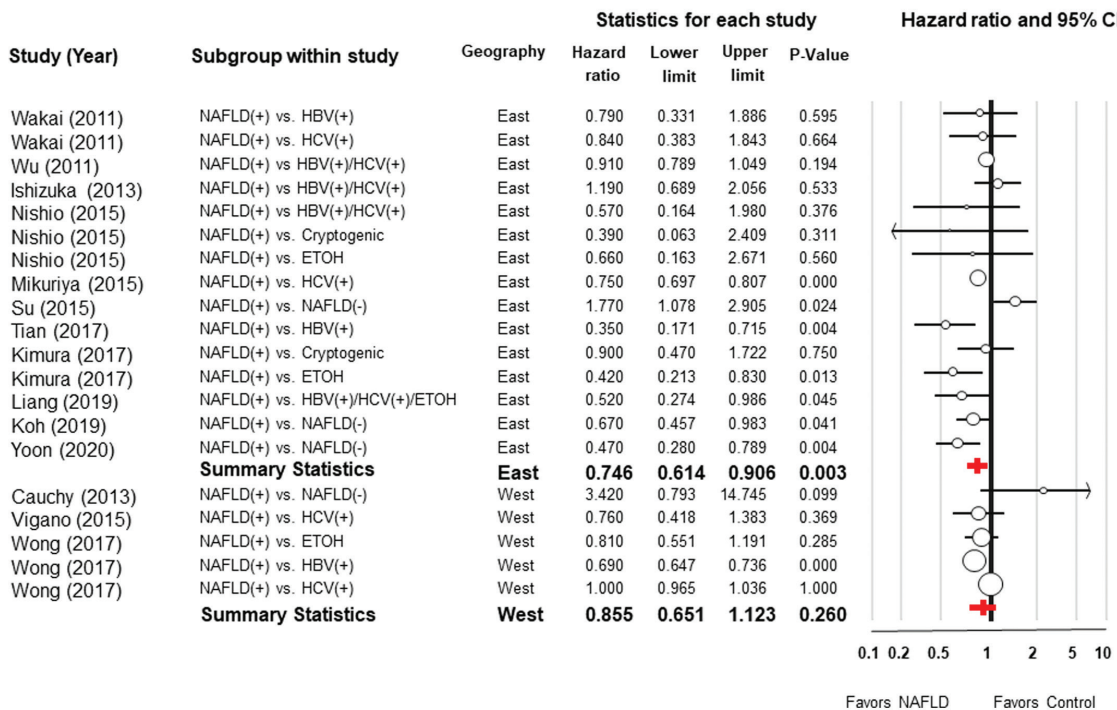


Figure 5. Panel A, Forest plots of meta-analysis with random effect model of the disease-free survival (DFS), and Panel B, overall survival (OS), of patients with nonalcoholic fatty liver disease (NAFLD) after hepatic resection for hepatocellular carcinoma compared to patients with other risk factors. Subgroup analysis was performed based on the geographical area where patients were enrolled.

The data used for this meta-analysis was extracted from observational studies with very high scores of the NOS indicating good quality.⁴⁴ Although all the articles had similar study designs, inclusion and exclusion criteria, indications for surgery, interventions, and duration of follow-ups, we found that they had significant variability as indicated by the high values of the I² statistics. Several reasons might have contributed to

this heterogeneity. Patients had comparable tumors and equivalent treatments, but their enrollment occurred over 25 years and in centers located in different continents. Over time, patient selection, operative techniques, and perioperative therapies had improved, and we suspect that the combination of all these factors might have contributed to the degree of heterogeneity that we observed in this meta-analysis.

Also, most studies (73%) were from Asia, 3 from Europe, and only 1 from the United States. Therefore, it is conceivable that distinct patient and tumor characteristics, as well as differences in the clinical management of patients, were responsible for the overall heterogeneity. To better understand the impact of these factors, we performed subgroup and meta-regression analyses to investigate how the pooled HRs changed based on the geography, the year of publication, and the prevalence of cirrhosis in the 2 groups. Since the quality of the studies was homogeneous, sensitivity analysis based on the quality of the studies was not done.

Geography

Asian patients represented the majority of the population. Oncological and clinical variations between Eastern and Western populations have been well described by other investigators.⁵⁵ Differences involve not only the predisposing factors for HCC⁵⁶ but also the genomic profile of the tumors,^{57,58} the clinical characteristics of the patients,^{59,60} and how they are managed by their healthcare providers.⁶¹

From the surgical point of view, Asian surgeons tend to have a more aggressive approach than surgeons practicing in Western countries.^{4,62} For example, in Asia, surgical resections are often performed even in the presence of multifocal HCCs and in patients with cirrhosis or portal hypertension as long as the liver function and the future liver remnant volume are satisfactory.^{63–65}

From the point of view of the tumor characteristics, Asian patients are affected by HCCs at a younger age, are more often affected by tumors with poor tumor cell differentiation, higher p53 expression,⁶⁶ and have a better prognosis than non-Asian populations.⁶⁷

Sensitivity analysis showed that the DFS favored NAFLD patients in Asia (HR = 0.73; 95% CI: 0.62–0.87; $P < 0.001$), while there was no significant difference between the 2 groups in studies from Europe and North America (HR = 1.045; 95% CI: 0.80–1.35; $P = 0.74$).

Similar findings were observed for the OS that favored Asian patients with NAFLD (HR = 0.746; 95% CI: 0.61–0.90; $P = 0.003$), while there was no survival difference between the 2 groups when only studies from Europe and North America were included (HR = 0.85; 95% CI: 0.65–1.12; $P = 0.26$).

The lack of significant differences between the 2 groups in Western countries might be due to an insufficient number of patients as well as the possibility that NAFLD patients from Europe and the United States had different clinical or tumor characteristics than Asian patients. Unfortunately, we were unable to further explore this aspect due to the lack of more granular data from the original studies.

Year of Publication

The OS advantage of NAFLD patients was more pronounced for studies performed in more recent years. This effect was appreciated by the presence of a negative linear correlation between the year of publication and the log of the HR of the OS of NAFLD patients. When studies published before 2015 were included, the difference in the OS between the 2 groups was not significant (HR = 0.93; 95% CI: 0.73–1.19; $P = 0.58$). On the other hand, analysis of the data from studies published after 2015 showed a significant OS advantage for NAFLD patients with an HR of 0.67 (95% CI: 0.51–0.83; $P < 0.001$).

A possible reason for the negative correlation between the HR and the year of publication was that over the years, surgeons and other healthcare providers might have gained more experience in how to manage and select patients with NASH who are more often affected by cardiopulmonary and other

metabolic conditions that increase their risk of postoperative mortality.^{68,69}

Prevalence of Cirrhosis

Opposite to patients with other risk factors, 10% to 75% of NAFLD patients develop HCCs in the absence of cirrhosis.^{69–71} Since cirrhosis is a major risk factor for perioperative mortality and long-term survival,^{39,72,73} we performed a meta-regression to test if cirrhosis was an important effect modifier. Contrary to our expectations, cirrhosis did not modify the results of this meta-analysis. We suspect that this negative finding was probably due to the similar prevalence of cirrhosis within the two groups. Consequently, our study was underpowered to detect differences in patient survival based on the presence or absence of cirrhosis and further investigations will be necessary to address this issue.

Strengths and Limitations of This Study

One of the strengths of this meta-analysis is the high quality of the included studies and the rigorous methodology used for the extraction of the data and the subgroup and meta-regression analyses performed to assess the impact of predefined effect modifiers.

The protocol used to conduct this meta-analysis was developed and registered before starting the systematic review of the literature, the extraction of the data, and the statistical analyses. Therefore, misleading post hoc analyses were avoided as they were not part of the published protocol.⁷⁴ Another strength was the assistance of 2 experienced health-science librarians who independently performed the systematic search of the literature that decreased the risk of missing relevant evidence. The systematic review of the literature identified a very large number of studies that were screened by 2 independent investigators to ascertain that all suitable articles were appraised. These efforts led to the inclusion of a large number of patients that enhanced the precision of the summary estimates.

Additional strengths were the use of dual data extraction and dual data entry to avoid the risk of incorrect transcription of the variables of interest.

Despite these strengths, some limitations should be noted. Ideally, individual patient data are preferable to aggregate data for the assessment of interactions. We believed that the likelihood of accessing the original data of studies performed over 25 years was very low; therefore, we did not make any attempt to obtain individual patient data from the primary investigators.

Also, we were unable to identify data from unpublished sources or the gray literature, and some evidence might have been involuntarily overlooked. Another limitation is that all the data used for this meta-analysis were from retrospective studies. Therefore, the risk of biases inherent to the original studies could not be completely adjusted. We also found significant heterogeneity among studies, probably due to differences in patients' characteristics, tumor factors, and the changes in the clinical management that have inevitably occurred over time. Finally, most studies were from centers located in Asia, and the results of this meta-analysis might not fully apply to patients from non-Asian countries.

CONCLUSIONS

The present meta-analysis represents the most comprehensive review of the literature on the outcomes of patients with NAFLD undergoing radical hepatic resections for HCC.

The results of this study suggest that after radical resections, NAFLD patients have more favorable DFS and OS in comparison to patients with other risk factors for HCC.

The longer survival of NAFLD patients was not contingent on the risk factors affecting the control group. Although these results might be due to the fact that cirrhosis is less common in patients with NAFLD compared to patients with other risk factors, our analysis failed to show that cirrhosis was an important effect modifier. However, further studies will be necessary to confirm this observation.

The current review also demonstrates that most studies on the outcomes of hepatic resections for HCC are from Asia. Therefore, there is the need for more studies from Western centers to better characterize the outcomes of non-Asian patients after hepatic resections for HCC in the settings of NAFLD.

Acknowledgments

M.M. designed the study, extracted the data, assessed the quality of the studies, did the statistical analyses, and wrote the manuscript. C.K. drafted the manuscript, and reconciled discrepancies between reviewers. P.B.-S. did the literature search and screening, extracted the data, assessed the quality of studies, and critically reviewed the manuscript. H.L., S.D., B.E., H.A.H., D.G., A.T., C.H., A.H., and R.B. critically revised the manuscript. C.W. performed the literature search. M.L.K. performed the literature search. S.T. critically reviewed the manuscript. J.B. reviewed the protocol, was the content expert, and critically reviewed the manuscript.

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