Gender and Regional Disparities in Incidence of Hepatocellular Carcinoma in Autoimmune Hepatitis: A Systematic Review and Meta-analysis

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Abstract

Background

Recent studies have identified an increased risk of hepatocellular carcinoma (HCC) in autoimmune hepatitis (AIH). Gender and regional disparities in incidence of HCC in AIH continue to be reported worldwide. Nevertheless, the magnitude of this gap remains unknown.

Method

We searched several databases including PubMed, Embase, Web of Science, Cochrane Library, Wangfang Data, CNKI and Sinomed. Incidence rates of HCC in AIH were combined and analyzed following the EBayes method. Incidence rate ratios were pooled to assess the gender differences. The impact of population difference, gender, age, cirrhotic condition was further analyzed with subgroup analysis and linear regression analysis.

Result

39 studies meeting our eligibility criteria were chosen for the analysis. The pooled incidence rate of HCC in AIH was 3.54 per 1,000 person-years (95%*CI* = 2.76–4.55). Pooled *IRR* for the risk of HCC in male AIH patients compared to female was 2.16 (95%*CI* = 1.25–3.75), with mild heterogeneity among studies. The pooled HCC incidence rate in AIH by continents was as follows: Europe 2.37 per 1,000 person-years (95%*CI* = 1.45–3.88), Asia 6.18 per 1,000 person-years (95%*CI* = 5.51–6.93), North America 2.97 per 1,000 person-years (95%*CI* = 2.40–3.68), Oceania 2.60 (95%*CI* = 0.54–7.58). The pooled HCC incidence rate in AIH related cirrhosis by continent was as follows: Europe 6.35 per 1,000 person-years (95%*CI* = 3.94–10.22), Asia 17.02 per 1,000 person-years (95%*CI* = 11.18–25.91), North America 10.89 per 1,000 person-years (95%*CI* = 6.69–17.74).

Conclusion

A higher HCC incidence in AIH was observed among male and in Asian populations. Routine HCC surveillance is cost effective for patients with AIH cirrhosis, especially for those in Asian populations.

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer in adults, accounting for about 75% of cases.[1] Nowadays, HCC has become the seventh most commonly diagnosed cancer and the fourth leading cause of cancer death all over the world.[2] HCC tends to cause no symptoms or negligible malaise at an early stage but grows aggressively with a high rate of metastasis, so most patients are diagnosed at the advanced stage and treatment options are limited. Major risk factors for HCC such as chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), carcinogens and inherited diseases have been worked thoroughly. However, there is a growing realization that some uncommon conditions such as metabolic syndrome (diabetes and obesity), diet-related liver disease

(alcoholic liver disease and non-alcoholic fatty liver disease) and autoimmune liver disease are strongly related to increased risk of HCC. A detailed understanding of different risk factors is crucial to improving the screening, early detection, prevention, and management of HCC.

Autoimmune hepatitis (AIH) is a female-dominated chronic liver disease caused by autoimmune-mediated inflammatory disorder, characterized by interface hepatitis, hypergammaglobulinemia, circulating autoantibodies and a favorable response to immunosuppression.[3] The initiation of abnormal autoimmunity is possibly relevant to the loss of tolerance against the patient's own liver antigens, but the mechanism is still unclear. Nevertheless, there have identified some risk factors, such as history of viral infections (Hepatitis A, Epstein-Barr, human herpes 6, measles), administration of drugs or herbals, other concurrent autoimmune diseases.[4] AIH is a relatively rare disease. The latest meta-analysis reported a pooled worldwide annual prevalence of AIH as 17.74 (95%*CI* = 12.01–22.87) per 100,000 persons. A higher prevalence was observed in European and American than in Asian populations.[5] Akin to any other chronic liver disease, AIH may progress to cirrhosis and even HCC. Recent studies have identified an increased risk of HCC in AIH. The standardized incidence rate (SIR) ranged from 8.24 to 28.98 and the standardized mortality rate (SMR) ranged from 20.56 to 42.30. [6–11] There is an inclination for females to develop AIH. Moreover, HCC incidence rates in AIH patients varied in different regions. Nevertheless, the gender and regional disparities in HCC risk among patients with AIH have not been studied yet.

Estimates of the incidence rate in specific population are a key indicator of cancer burden, which is beneficial to formulating a more accurate strategy for the management of HCC. Thus, to better understand the disparities, we summarize all available evidence and perform a meta-analysis to clarify the issues.

Materials And Methods

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [12] The systematic review was prospectively registered at PROSPERO (www.crd.york.ac.uk/PROSPERO) as CRD42020157000.

Data Sources and Searches

We searched several databases including PubMed, Embase, Web of Science, Cochrane Library, Wangfang Data, CNKI and Sinomed from the inception of the databases through December 23, 2020. The search strategy included subject terms (“autoimmune hepatitis”) AND (“hepatocellular carcinoma” OR “malignancies” OR “outcome”) AND (“incidence” OR “prevalence” OR “risk factors” OR “case-control studies" OR “cohort studies” OR “review”) and their related synonyms. We also retrieved the references of the included publications and related reviews manually.

Eligibility Criteria

Two reviewers (L.-J. Y. and S.-Y. Y.) determined the suitability of articles for further review independently by performing an initial screen of abstracts or titles. We included studies meeting the following criteria: (1) Observational studies (prospective or retrospective) reported incidence rates of HCC in AIH or provided sufficient raw data to calculate incidence rates; (2) AIH patients did not suffer from chronic viral hepatitis such as hepatitis B, hepatitis C. If two or more studies reported the statistics based on the same cohort, we excluded those with a smaller number of AIH patients.

Data Extraction and Quality Assessment

Data was extracted from included studies by two reviewers (L.-J. Y. and G.-X. M.) independently. Disagreement was discussed with another reviewer (K.-X. L.). We extracted the following information from every single included study: year of publication, country where the study performed, population source, study period, follow-up period, number of participants, number of HCC patients with AIH, gender distributions of AIH patients with or without HCC. We estimated the quality of included studies according to the Newcastle-Ottawa scale, which comprised three sections: selection (up to 4 points), comparability (up to 2 points) and outcome (up to 3 points), with a maximum of 9 points.

Data Synthesis and Analysis

We collected incidence rates of HCC in AIH patients per 1,000 person-years with 95% confidential interval (CI). For studies only provided raw data, obeying Poisson distribution, we calculated the incidence rates. A correction factor of 0.5 was used for both the number of HCC cases and total person-years of follow-up under the circumstances when HCC counts were zero. Incidence rates of HCC in AIH patients were combined and analyzed following the EBayes method. Provided the between-study heterogeneity was substantial, we performed the meta-analysis using a random-effects model. If not, we used a fixed-effects model. For studies reported the data on HCC incidence rate in AIH patients by gender, incidence rate ratios were pooled to assess the gender differences. Furthermore, we combined and summed the incidence rates of HCC in AIH patients in different countries to figure out if there existed regional disparities. We extracted the prevalence of AIH in different countries from the latest study performed by *Tingting Lv et al.*[5]. An average risk value, the product of overall prevalence of AIH worldwide and pooled incidence of HCC in AIH patients, was set up to distinguish the high-risk region. Heterogeneity was assessed using the Cochrane Q statistic and I^2 statistic for each combined analysis, with $P < 0.1$, $I^2 > 50\%$ indicating significant heterogeneity between studies. Publication bias was assessed by the Egger's test and Begg's test. Meta-analysis was performed using the Stata software version 16.0 (Stata Corporation, College Station, TX, USA).

Result

Literature Search

We identified 1,498 citations according to the search strategies. After removal of duplicates, the remaining pool of articles was left with a tally of 1,111. Of these citations, 937 were excluded for their

irrelevance by screening the titles and abstracts. The remaining 174 citations were evaluated by full-text reviewing. Finally, 39 studies (35 published in English, 4 published in Chinese) meeting our eligibility criteria were chosen for the analysis, which comprised of 28 original articles and 11 abstracts, involving 14,597 AIH patients. (**Supplementary Fig. 1**)

Quality Assessment

The detailed NOS items and scores of each study were shown in **Supplementary Table 2**. Of 39 studies, only 11 studies provided the data to assess the risk between different gender and the item comparison could be evaluated. We ranked the quality of original studies as three level. We labelled the studies scoring 6–7 as high quality, 4–5 as moderate quality, 0–3 as low quality for the non-comparative studies. As to comparative studies, we labelled the studies scoring 7–9 as high quality, 4–6 as moderate quality and 0–3 as low quality. Eighteen studies were regarded as high quality. Twenty studies were regarded as moderate quality. Only one study, *Macaron 2010*[13], was regarded as low quality. Most studies derived the subjects from a single medical center or several medical centers, which might affect the representativeness of the result.

Baseline Characteristics of Included Studies

Characteristics of included 39 studies were shown in **Supplementary Table 1**. Among them, 16 studies were performed in Europe (5 from UK, 2 from Germany, 2 from Denmark, 2 from Sweden, Belgium, Greece, Netherland, Spain and Italy each contributed one study) and 14 studies were performed in Asia (7 from Japan, 5 from China, India and South Korea each contributed one study) and 8 studies were performed in North America (all of them were from USA) and only one study was from Oceania (New Zealand). There was no published study conducted in Africa or South America after our thorough retrieval. Except for 6 studies that did not report the population source, most studies collected data of AIH patients in tertiary medical centers (17 in single center and 13 in multicenter), while only 3 studies reported data covering the general population. The mean follow-up time ranged from 15.1 to 149.6 months. All the cohorts showed a predominance of female, with a median percentage of females in AIH patients as 83%.

HCC Incidence Rate in AIH Patients

The overall pooled HCC incidence rate in AIH patients was provided in **Supplementary Fig. 2**. Only 3 studies reported no newly diagnosed HCC at the end of the follow-up, so the incidence rate was calculated with a correction factor. The meta-analysis contained records on 14,597 patients, among whom 426 developed HCC during follow-up. The pooled incidence rate of HCC in AIH patients was 3.54 per 1,000 person-years (95%*CI* = 2.76–4.55). We detected substantial heterogeneity in the analysis (I^2 = 76.9%, P < 0.01). To explore the study heterogeneity, we investigated the influence of each individual study on the overall meta-analysis summary estimate and found that *Hiromasa Ohira et al. 2013* was suspected of excessive influence. (**Supplementary Fig. 3**) After removal of *Hiromasa Ohira et al. 2013*, the Q-value assessing heterogeneity achieved a 38% reduction (Q-value went down from 122.784 to 76.534).

Publication bias was examined by Begg's test and no publication bias was detected. (**Supplementary Fig. 4**)

Gender Disparities

Fifteen studies provided data on the HCC incidence rate in AIH patients by gender. The pooled HCC incidence rate was 3.446 per 1,000 person-years (95%*CI* = 2.439–4.870) in female patients and 4.053 per 1,000 person-years (95%*CI* = 2.410–6.816) in male patients, both with mild between-study heterogeneity. (Fig. 1A) Eleven studies were available to calculate the incidence rate ratio(IRR). Pooled *IRR* for the risk of HCC in male AIH patients compared to female was 2.16 (95%*CI* = 1.25–3.75), with mild heterogeneity among studies. (Fig. 1B) When stratified by continent, the risk of HCC in male AIH patients was significantly higher than female among populations in North America while there was no significant difference in Europe and Asia subgroups. (Fig. 1C) The pooled HCC incidence rate by gender in different continents was listed in **Supplementary Table 3**.

Regional Disparities

The incidence rate of HCC in AIH patients in individual countries was provided in Fig. 2 and the details were demonstrated in **Supplementary Table 4**. The product of overall prevalence of AIH worldwide and pooled incidence of HCC in AIH patients was 52.60, which was regarded as average risk value. Eight countries (America, Denmark, Japan, New Zealand, South Korea, Spain, Sweden and The Netherlands) were available to calculate a risk value by multiplying the national prevalence of AIH and HCC incidence rate in AIH patients. Two countries, Japan and New Zealand, were identified as high-risk regions with values of 146.29 and 67.91 respectively. The risk values of the remaining 6 countries were all below average. The pooled HCC incidence rate in AIH patients according to continents was as follows: Europe 2.37 per 1,000 person-years (95%*CI* = 1.45–3.88), Asia 6.18 per 1,000 person-years (95%*CI* = 5.51–6.93), North America 2.97 per 1,000 person-years (95%*CI* = 2.40–3.68), Oceania 2.60 (95%*CI* = 0.54–7.58, only contained one study). (Fig. 3A) Substantial heterogeneity was detected in Europe subgroup, while analyses in Asia subgroup and North America subgroup both showed merely mild between-study variance. A total of 16 studies provided the statistics on HCC incidence in patients with evidence of cirrhosis at AIH diagnosis. The pooled HCC incidence rate in AIH-cirrhosis patients by continent was as follows: Europe 6.35 per 1,000 person-years (95%*CI* = 3.94–10.22), Asia 17.02 per 1,000 person-years (95%*CI* = 11.18–25.91), North America 10.89 per 1,000 person-years (95%*CI* = 6.69–17.74). All three subgroup meta-analyses showed mild between-study heterogeneity.(Fig. 3B)

The summary of potential factors related to the regional disparities was shown in **Supplementary Table 3**. Studies from Asia had higher proportion of females, older mean age of patients and lower proportion of cirrhosis at AIH diagnosis in cohorts. AIH patients, whether male or female, had higher incidence of HCC among Asian than among European and American populations. Thus, we further explored the correlation between three covariates and HCC incidence using single-factor linear regression and multiple-factors linear regression and found that only the proportion of patients with cirrhosis in AIH

cohorts was positively associated with the HCC incidence. (single-factor linear regression: $p = 0.018$) (**Supplementary Table 5**)

Discussion

There has been uncertainty about the risk of HCC in AIH patients between different gender and among various regions. To address the issues, in this systematic review, we assembled data from 39 observational studies reporting the HCC incidence rate in AIH patients. The incidence rate varied strikingly, from 0.75 to 10.02 per 1,000 person years according to the geographical location of the population under study. After analysis, we found that an overall HCC incidence rate of 3.54 per 1,000 person-years (95%*CI* = 2.76–4.55) among patients with AIH.

Our study confirmed the risk of HCC in male patients with AIH was over 2-fold higher than in female ones. Moreover, globally, we revealed a higher incidence rate of HCC in AIH patients among Asian populations, compared to those from Europe, Oceania or North America. The regional disparities were consistent when we combined the incidence rate in different gender by continent. When it came to AIH patients accompanied with cirrhosis, we found that cirrhosis status at AIH diagnosis was significantly associated with an increased incidence rate for HCC, which was much more pronounced among Asian populations.

To further explore the factors related to the disparities, we estimate the association between three covariates (percentage of female in AIH patients, percentage of AIH patients with cirrhosis at index, mean age of patients at AIH diagnosis) and HCC incidence respectively. Consequently, we found that the proportion of AIH patients with cirrhosis at index was positively associated with HCC incidence. However, surprisingly, the studies in Asia had relatively lower proportion of AIH-cirrhosis patients, which implied the regional disparities might not result from the initial cirrhotic condition of the cohorts.

We made a combination of the HCC incidence in AIH patients and AIH prevalence to estimate every single country. After analysis, we deduced there might exist more HCC patients evolved from AIH in Japan and New Zealand. Unfortunately, the risk value could not be calculated in all countries owing to lack of statistics on AIH prevalence. The HCC incidence rate among AIH patients in India and China ranked in the top two places. As we all know, India and China are the two most populous countries in the world, which are bound to possess a large population of AIH patients no matter the AIH prevalence. Thus, even though we failed to confirm the exact risk value, we recommended that clinical workers should pay more attention to the AIH patients in India and China. Previous meta-analysis reported the overall pooled incidence of patients with AIH cirrhosis was 1.007% per year (10.07 per 1,000 person-years).[14] According to the latest cost-benefit analysis, an HCC incidence > 0.4% per year was necessary for ultrasound with serum AFP level to be cost-effective compared with no surveillance in patients with compensated cirrhosis.[15] The annual incidence rates of HCC in AIH related cirrhosis no matter in Asian, European and North American populations all exceeded 0.4%. (Asia: 1.7%; North America: 1.1%; Europe: 0.6%) Thus we recommended routine HCC surveillance for patients with AIH cirrhosis, especially for those in Asia.

Several limitations in our study should be mentioned. Of 39 studies involved in our analysis, there were 11 studies published as abstract, which provided limited information for us to estimate the validity of the methodology and the credibility of the result. Furthermore, the majority of the data were derived from single center and multicenter and only 3 of them reported the data on general populations, which might cause inaccuracy when we simply treated these data as representative for some countries. The inaccuracy could be exacerbated if there was merely one study involved and no combined analysis to reduce the bias. For example, such happens in the comparison among continents (Oceania). Almost all the studies involved, except for *Ohira 2013*, reported a small number of HCC cases that ranged from 0 to 15 during the follow-up period. Therefore, the estimates of incidence rate might not be precise. What's more, we found that there existed gender differences and global disparities but we failed to figure out the exact reason on account that the information from original studies was not sufficient for us to further explore the risk factors.

In summary, this systematic review and meta-analysis provides a comprehensive summary of the current literatures on the HCC incidence rate of AIH patients. A higher incidence was observed among male patients and patients in the Asian population. Further study should be committed to the cause of the disparities.

Conclusion

In conclusion, it is riskier for male AIH patients to develop HCC. AIH patients in Asia were at an increased risk for HCC. Routine HCC surveillance is cost effective for patients with AIH related cirrhosis, especially for those in Asia.

Abbreviations

HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; AIH, autoimmune hepatitis; SIR, standardized incidence rate; SMR, standardized mortality rate; NOS, Newcastle-Ottawa scale; CI, confidential interval; IRR, incidence rate ratio.

Declarations

Funding Information

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Conflicts of Interest

There are no conflicts of interest to declare.

Ethics Approval

Not applicable.

Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Data Transparency

The manuscript's guarantors (L.-J.Y. and T.L.) affirm that the manuscript shows an honest, accurate, and transparent study; that no important aspects of the study have been omitted and that any discrepancies from the study have been explained.

Author Contributions

All authors had full access to the data in the study and take responsibility for the integrity and authenticity of the data. L.-J.Y. formulated the study objective, conceptualized the study, performed the statistical analysis, and interpreted the results; K.-X.L. and G.-X.M. designed the protocol of the systematic reviews; Z.-R.D., J.-G.H., Z.-Q. C. provided important guidance to the protocols and modified them; L.-J.Y. and S.-Y.Y. assessed the availability of each study retrieved from online databases respectively and disagreements were identified and discussed with K.-X.L.; H.-C.L., and Z.-N.D. performed the methodology, data collection, and data validation; L.-J.Y. guided the task of formal statistical analysis and analysis of the data; L.-J.Y. and T.L. contributed to outlining the manuscript and drafting the manuscript; L.-J.Y. and T.L. verified the underlying data. T.L. supervised and coordinated the study. All authors have read and approved the final version.

References

1. Altekruse SF, Devesa SS, Dickie LA, McGlynn KA, Kleiner DE. Histological classification of liver and intrahepatic bile duct cancers in SEER registries. *Journal of registry management.* 2011;38(4):201-205.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians.* 2018;68(6):394-424.
3. Zachou K, Muratori P, Koukoulis GK, et al. Review article: autoimmune hepatitis - current management and challenges. *Alimentary pharmacology & therapeutics.* 2013;38(8):887-913.
4. EASL Clinical Practice Guidelines: Autoimmune hepatitis. *J Hepatol.* 2015;63(4):971-1004.

5. Lv T, Li M, Zeng N, et al. Systematic review and meta-analysis on the incidence and prevalence of autoimmune hepatitis in Asian, European, and American population. *Journal of gastroenterology and hepatology.* 2019;34(10):1676-1684.
6. Puustinen L, Barner-Rasmussen N, Pukkala E, Färkkilä M. Incidence, prevalence, and causes of death of patients with autoimmune hepatitis: A nationwide register-based cohort study in Finland. *Digestive and Liver Disease.* 2019;51(9):1294-1299.
7. Arinaga-Hino T, Ide T, Miyajima I, et al. Risk of malignancies in autoimmune hepatitis type 1 patients with a long-term follow-up in Japan. *Hepatology Research.* 2018;48(3):E222-E231.
8. Danielsson Borssén Å, Marschall HU, Bergquist A, et al. Epidemiology and causes of death in a Swedish cohort of patients with autoimmune hepatitis. *Scandinavian Journal of Gastroenterology.* 2017;52(9):1022-1028.
9. Castro FA, Liu X, Forsti A, et al. Increased risk of hepatobiliary cancers after hospitalization for autoimmune disease. *Clin Gastroenterol Hepatol.* 2014;12(6):1038-1045.e1037.
10. Ngu JH, Gearry RB, Frampton CM, Stedman CAM. Mortality and the risk of malignancy in autoimmune liver diseases: A population-based study in Canterbury, New Zealand. *Hepatology.* 2012;55(2):522-529.
11. Werner M, Almer S, Prytz H, et al. Hepatic and extrahepatic malignancies in autoimmune hepatitis. A long-term follow-up in 473 Swedish patients. *Journal of Hepatology.* 2009;50(2):388-393.
12. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology.* 2009;62(10):e1-34.
13. Macaron C, Hanouneh IA, Zein NN. Incidence and risk factors of hepatocellular carcinoma in patients with primary biliary cirrhosis. *Hepatology.* 2010;52(6):2240-2240.
14. Tansel A, Katz LH, El-Serag HB, et al. Incidence and Determinants of Hepatocellular Carcinoma in Autoimmune Hepatitis: A Systematic Review and Meta-analysis. *Clinical Gastroenterology and Hepatology.* 2017;15(8):1207-1217.e1204.
15. Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-Effectiveness of Hepatocellular Carcinoma Surveillance: An Assessment of Benefits and Harms. *The American journal of gastroenterology.* 2020;115(10):1642-1649.

Figures

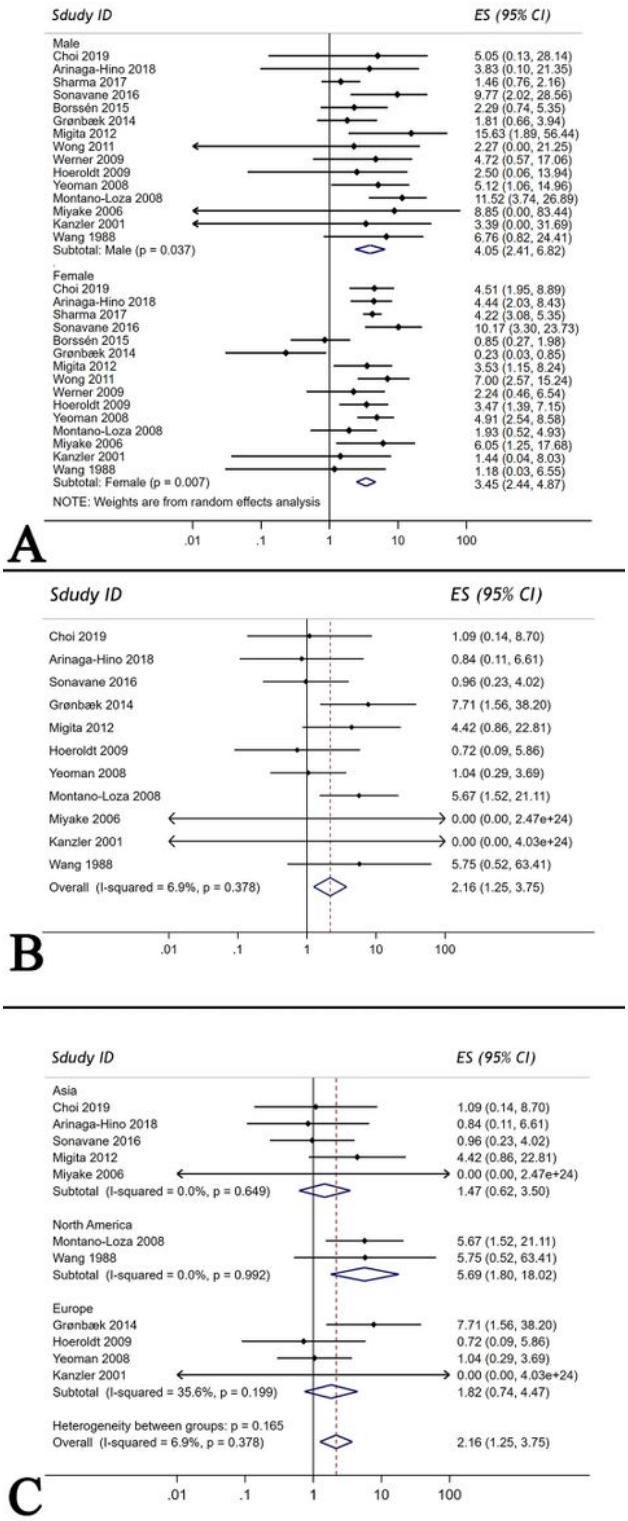

Figure 1

Forest plots of (A) HCC incidence rate in AIH patients by gender per 1,000 person-years; (B) Pooled IRR for the risk of HCC in male AIH patients compared to female; (C) Pooled IRR for the risk of HCC in male AIH patients compared to female stratified by continents.

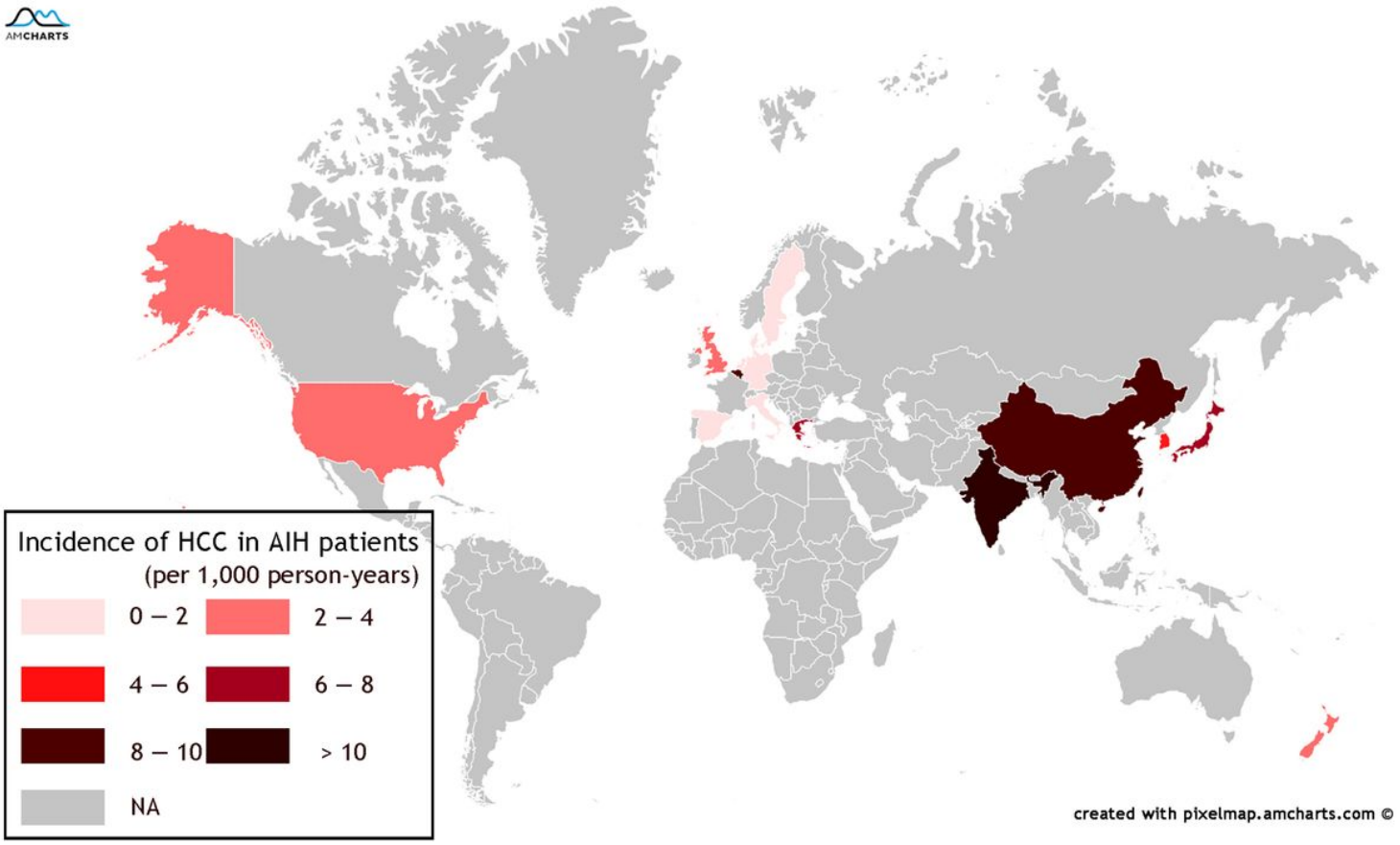

Figure 2

Incidence of HCC in AIH patients worldwide. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area o bbnhjr of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

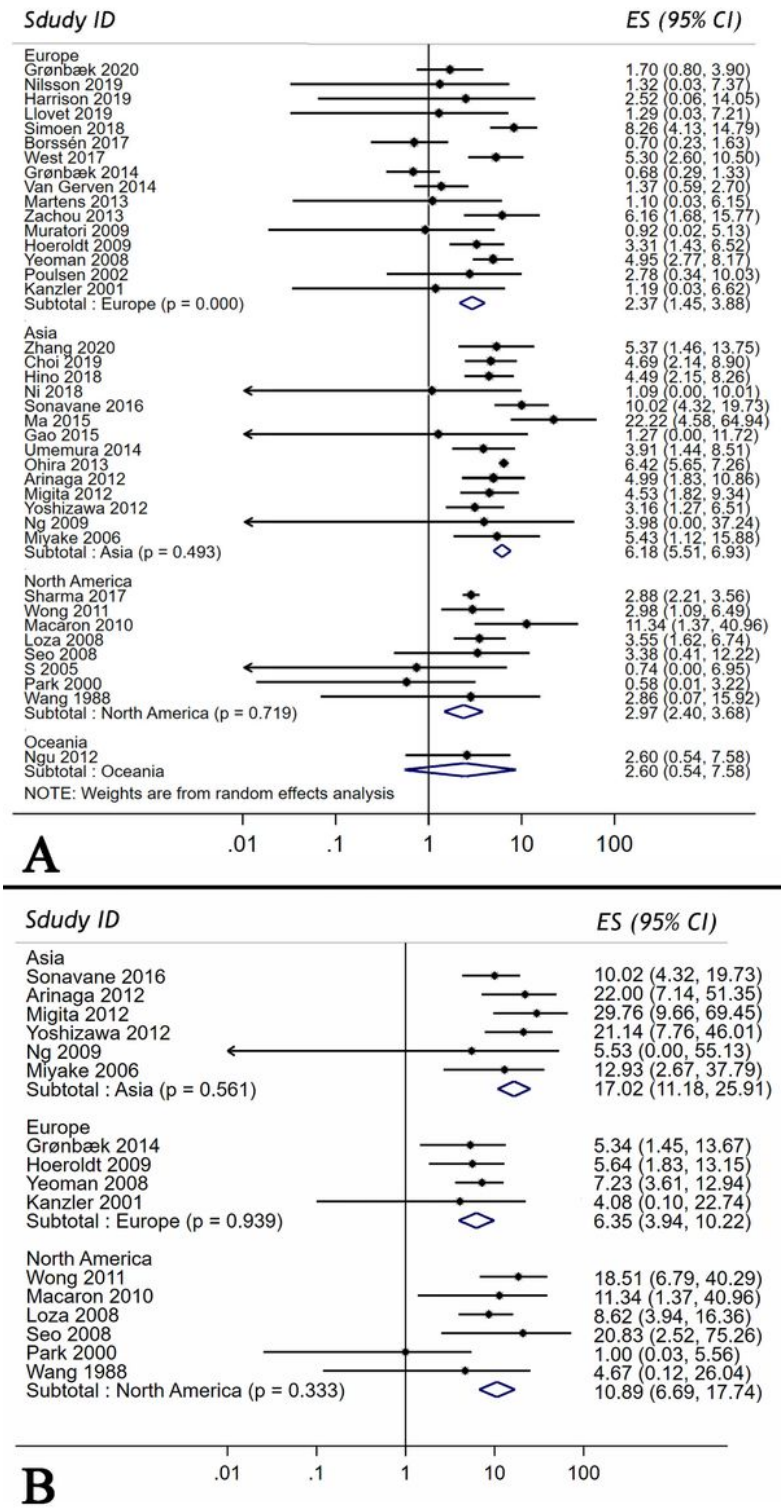

Figure 3

Forest plots of (A) Incidence rate of HCC in AIH patients by continents per 1,000 person-years; (B) Incidence rate of HCC in AIH-cirrhosis patients by continents.

Supplementary Files

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