Hepatocellular carcinoma in patients with autoimmune hepatitis – a systematic review of the literature published between 1989-2016

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Abstract

Background and aims. Liver cancer is one of the most common cause of deaths from cancer. Hepatocellular carcinoma (HCC) was reported at a frequency of 7% of patients with autoimmune hepatitis (AIH) - related cirrhosis in 1988. We aimed to provide a systematic literature review on the frequency of HCC in patients with AIH, after the discovery of hepatitis C virus (HCV), in order to avoid any possible confounding etiology.

Methods. A literature search of the PubMed database between 1989-2016 was performed, using the relevant keywords "hepatocellular carcinoma" and "autoimmune hepatitis". We followed the PRISMA statement guidelines during the preparation of this review.

Results. Eleven studies (n=8,460 patients with AIH) were retained for the final analysis. HCC was diagnosed in 0-12.3% of the AIH patients included in these studies. The overall occurrence of HCC in patients with AIH was estimated in two studies, at 5.1% and 6.2%, respectively. In patients with AIH and cirrhosis, the percentage of HCC varied between 0.2%-12.3%. The proportion of HCC in patients with AIH without cirrhosis was estimated at 1.03%. The percentage of cirrhosis in AIH patients varied from 18.7% to 83.3% in Japan, and from 12% to 50.2% in the other areas. The mean follow-up of the patients with AIH was of 10 years.

Conclusions. The development of HCC in patients with AIH appeared to be similar before and after the discovery of HCV, and it was mainly associated to cirrhosis. The number of patients developing cirrhosis in relation with AIH was impressive. The long evolution of AIH to cirrhosis and, eventually, to HCC, has been be suggested.

Keywords: hepatocellular carcinoma, autoimmune hepatitis, systematic review

Background and aims

Liver cancer is predicted to be the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide in 2018, with about 841,000 new cases and 782,000 deaths annually [1]. Primary liver cancer includes hepatocellular carcinoma (HCC) (comprising 75%-85% of cases) and intrahepatic cholangiocarcinoma (comprising 10%-15% of cases) as well as other rare types [1]. Hepatocellular carcinoma (HCC) registered the highest and the most rapid rate of increase in the recent period of time [2]. Cirrhosis of any etiology is a unanimously recognized risk factor for HCC.

Autoimmune hepatitis (AIH) appeared to be a rare cause of HCC in observational studies. It could have been even more rare after the discovery of hepatitis C virus (HCV), in 1989. HCC was reported at a frequency of 7% of AIH patients with cirrhosis of at least five years' duration, in 1988 [3] . In 2000, the same team found only 1% of the HCC patients having AIH–related cirrhosis, after the exclusion of the chronic infection with HCV [4]. In 2013, the frequency of HCC in patients with AIH and cirrhosis was estimated at 1% to 9%, and the annual occurrence in patients with cirrhosis at 1.1% to 1.9% [5].

The aim of our analysis was the evaluation of the frequency of HCC in AIH patients, according to the data published between 1989 and 2016.

Materials and methods

We conducted a systematic literature review following the PRISMA statement guidelines [6] (Figure 1).

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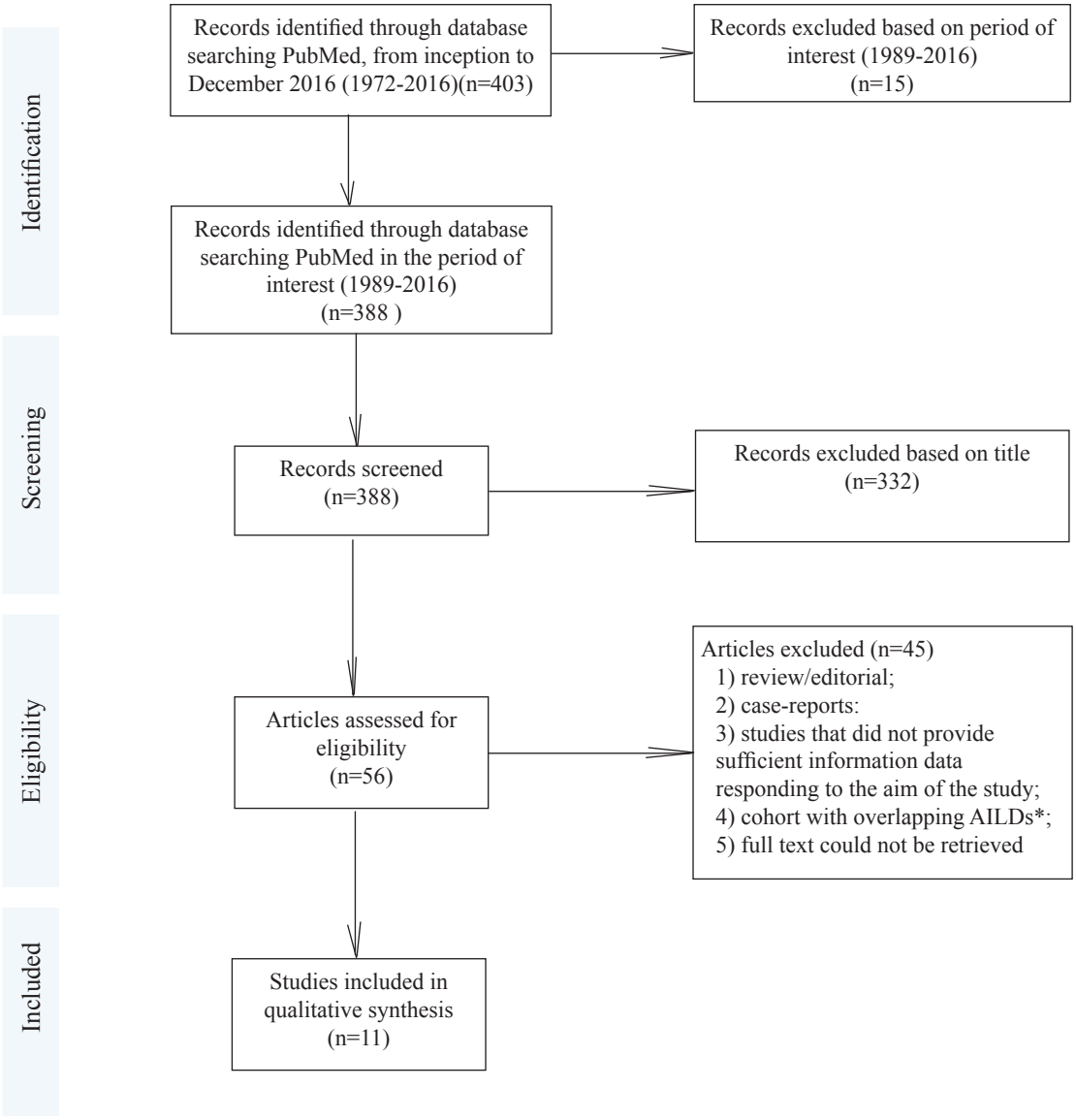

*AILDs: Autoimmune liver disease spectrum

Figure 1. PRISMA flow diagram of studies screening and selection.

Study selection

A literature search of the PubMed database 1989-2016 was performed, using the relevant keywords "hepatocellular carcinoma" and "autoimmune hepatitis", in order to identify the published studies that examined the frequency of HCC in patients with AIH. The back extension of the study was limited to 1989, when HCV was discovered. The authors screened the title and the abstract of the retrieved records for eligibility. The full-texts of the potentially eligible studies were reviewed for analysis. The search was conducted in Dec 2016 to Jan 2017.

We included original cohort studies and surveys, prospective and retrospective, published in peer-reviewed journals during the period 1989-2016, which evaluated the development of HCC in the context of AIH. In all the included studies, presence of an infection with hepatitis B and C viruses was excluded by serological tests. The studies were written in English language. A number of studies were excluded for various reasons: 1) review/editorial; 2) case reports: 3) studies that did not provide sufficient information data corresponding to the aim of the study; 4) cohorts with overlapping autoimmune liver disease spectrum (AILDs); 5) the full text could not be retrieved.

Data extraction

The following items were extracted from the selected studies: author, year of publication, number of AIH patients, patients with AIH-related cirrhosis (at any time during the period of follow-up), frequency of AIH-related HCC (number, percentage, other estimation), duration of follow-up of patients with AIH.

Results

The PubMed citations identified 403 articles, using the search terms "hepatocellular carcinoma"and "autoimmune hepatitis", from inception to December 2016 (1972-2016). In the period of interest, 1989-2016, a number of 388 articles were identified. A number of 56 were retrieved for analysis. Eleven English language studies (n=8,460 patients with AIH) were retained in the final analysis [4,7-16]. (Figure 1. PRISMA flow diagram of studies screening and selection).

Among the 11 studies included in the final analysis, 2 were declared as prospective [7,13] and 9 were declared as retrospective [4,8-12,14-16] studies. The 11 studies included a total number of 8,460 patients with AIH, with individual study cohorts counting from 180 patients [12] to 4869 patients [14]. One study [16] reported cumulative data from the same areal, estimated in two periods of time, in 2009 [10] and 2015 [16]. We considered this aspect in counting the total number of patients included in the analysis. Only the cohort 2015 was included. We retained the two studies [10,16] because they offered an interesting insight as regards HCC related to AIH, estimated as a longitudinal observation (years 2009 and 2015), in the same areal.

The summary of the included studies and their results [4,7-16] are shown in Table I.

The range of HCC frequency in patients with AIH varied in individual studies from 0 [9] to 12.3% [7].The overall percentage of HCC in patients with AIH was estimated in two studies, at 5.1% [14] and at 6.2% [7], respectively. In patients with AIH and cirrhosis, the percentage of HCC varied between 0.2% to12.3% [4,7-13,15,16]. One study mentioned the proportion of HCC in patients with AIH without cirrhosis, at 1.03% [13]. The mean follow-up of patients with AIH was of 10 years (ranging from 1 to 44 years [4,7-16]. The percentage of cirrhosis in AIH patients varied from 18.7% to 83.3% in Japan [12-14], and from 12% to 50.2% in the other areas [4,7-11,15,16]

Table I. Characteristics of the included studies. HCC frequency among patients with AIH – individual studies analytical aspects [4,7-16]

Reference	AIH Cases No	AIH-cirrhosis at any time of surveillance (no.patients and/or (%)	HCC estimates (no.patients, %, other, context)	Follow-up AIH Mean* (month/years)/ other estimation
Park SZ, et al (2000) [4]	212	88 42%	0.5% of AIH 1% of AIH cirrhosis	123±9month
Yeoman AD, et al (2008) [7]	243	122 50.2%	15/243 6.2% of AIH 12.3% of AIH cirrhosis incidence 1.1% /year	11 years (1-36)
Montano-Loza AJ, et al (2008) [8]	227	78%	9/227 4% of AIH cirrhosis	122month (12-372) Interval to HCC development: 136±13 month
Teufel A, et al (2009) [9]	278	89 (32%)	AIH cohort : 0 <0.2% per patient-AIH cirrhosis-year	8.6years (0-34)
Werner M, et al (2009) [10]	473	30%	0.6% of AIH cirrhosis	8.8years
Wong JR, et al (2011) [11]	322	50	6/50 of AIH cirrhosis 1.9%/year	10.0years
Hino-Arinaga T, et al (2012) [12]	180		6/180 3.3% of AIH 5/6 (83.3%) AIH cirrhosis	80.2month
Migita K, et al (2012) [13]	193	21 (10.9%) + 15 (7.8%)	7/193 3.6% 2/193 of AIH (1.0%) 5/193 of AIH cirrhosis (2.6%)	8±4.5years
Ohira H, et al 2013)[14]	4869	77.9%	5.1% of AIH	8 (0-29)years
van Gerven NM, et al (2014) [15]	1313	12%	1% of AIH cirrhosis	8 (0-44)years
Danielsson Borssén Å, et al (2015) [16]	634	248 (39%) 179 (28%) at AIH diagnosis 69 (11%) during follow-up	10 cases 4% of AIH cirrhosis Incidence 0.3%	Time between diagnosis of cirrhosis and HCC 12 (0-29) years

*Follow-up: the mean period from AIH diagnosis to the detection of HCC

Two of the identified studies reported results as regard to HCC in AIH patients in the same areal, as longitudinal observations (years 2009 and 2015) [10,16]. HCC was recorded in 0.6% of AIH cirrhosis patients in 2009 [10], and in 4% of AIH cirrhosis patients in 2015 [16]. The estimated incidence in 2015 was 0.3% [16].

Discussion

Given the importance of the HCC for the public health, it is of high importance to prevent it. The prevention is based on the identification of the liver diseases leading to HCC. AIH is an unusual etiology but it also should be considered and identified. We undertook this literature survey starting with the year of HCV discovery, in order to avoid inclusion of patients with this etiology in our search.

The present study analysis suggest that the proportion of HCC in AIH patients is similar to that recorded before the discovery of HCV [4,7-16]. This aspect poses many problems. One of these is related to the accurate exclusion of occult viral hepatitis B and C [17]. Other problems are related to other possible etiologies of AIH and of cirrhosis, and, eventually, of other viruses/other risk factors inducing autoimmune hepatitis/autoantibodies. An interesting issue could be to find which are the intervening risk factors that completed this 'etiological gap'.

In 1988, HCC was reported in 7% of the AIH patients with cirrhosis of at least five years' duration [3]. In 2000, the same team found only 1% of patients with HCC among the patients with AIH–related cirrhosis, after excluding those with HCV infection [4]. The frequency of HCC in patients with AIH and cirrhosis was estimated at 1-9%, and the annual occurrence in patients with cirrhosis at 1.1-1.9%, in 2013 [5].

The HCC developmental probability in AIH patients, with or without cirrhosis, was estimated [12]. The 10-year probability to develop HCC was estimated at 15%, and the 20-year probability at 23%, in patients with liver cirrhosis at the time of AIH diagnosis. The 10-year probability to develop HCC was 0 and the 20-year probability was 16% in patients without liver cirrhosis at the time of AIH diagnosis [12]. The percentage of cirrhosis in AIH patients seemed impressive (4,7-16). The advanced stage of cirrhosis and its long duration have been considered predictors of HCC in AIH patients [5].

Apart of its relation to HCV, the present literature review confirmed the previous known ascertained facts about AIH-related HCC. HCC occurred relatively rarely in the context of AIH. HCC developed in long standing AIH, mainly in patients with cirrhosis. Cirrhosis appeared as a *sine qua non* condition for the development of HCC in AIH-patients. A long time of evolution of AIH towards cirrhosis and, eventually to HCC, has been suggested [5]. This aspect could be explained by the fact that we used, at least in part, the same data base. Even the incidence of AIH is apparently low, its prevalence could be not negligible in relation to the development of complications, such of cirrhosis and HCC.

Etiology of the underlying cirrhosis and the risk of HCC

HCC developed in more than 90% of patients on the setting of cirrhosis of different etiologies. The impact of HCV infection and HCV-related autoantibodies altered the findings on AIH-related HCC before the discovery of HCV in 1989 [4]. Many studies suggested that the patients with AIH, and especially those with AIH-related cirrhosis, could develop HCC [4,5].

The variable risk of malignancy among different etiologies of liver cirrhosis may reflect the variation in cancer risk inherent to the primary disease [11]. The etiology of cirrhosis influenced the risk of HCC. In 2009, based on previous studies, the HCC incidence per year (%) in patients with AIH-related cirrhosis was estimated to be the lowest (<0.2%), as compared to cirrhosis of other etiologies, such as HBV cirrhosis (1-15%), HCV cirrhosis (1-8%), alcoholic liver disease (1%), hemochromatosis (2-6%), primary biliary cirrhosis (2%) [9].

Other estimates, in 2011, suggested a 1.9% prevalence of HCC in patients with cirrhosis due to AIH, and suggested that it might be comparable to the HCC risk in cirrhosis caused by viral hepatitis or with other etiologies [11,17]. Estimates from 2015 noted an incidence of HCC in patients with AIH of 0.56% to 1.9% in Europe and America, and of 0.45% to 0.64% in Asia Pacific region [18].

After the discovery of HBV-DNA sequences in tumor samples from patients negative for serum HBsAg, the problem of an occult hepatitis B infection was revealed. As a consequence, the necessity for screening the patients for antibodies to hepatitis B core antigen (HBcAb) was emphasized [17]. Moreover, it has been reported that even in patients who tested negative for serum HBV-DNA and HCV-RNA, liver tissue samples frequently tested positive for HBV-DNA or HCV-RNA, and this could favor the development of HCC [4,19-21]. Studies on the mechanisms of HBV/HCV infection implication in the development of HCC, and the identification of more subtle markers of infection are ongoing [22-25]. These new findings could eventually explain why the frequency of HCC related to AIH did not change significantly with the use of the common serological screening tests for HBV and HCV infections, the hepatitis B surface antigen (HBsAg) and antibodies anti-HCV (anti-HCV), respectively.

Several mechanisms explaining the development of HCC from autoimmune liver diseases have been proposed: enhanced progression to cirrhosis through progressive autoimmune hepatitis, decreased antitumor immune response caused by the therapy with steroids and immunosuppressants, or virus related hepatitis [19].

In the same time, the rare occurrence of HCC in AIH patients, even in long-standing cirrhosis, remained unexplained. The development of HCC could be simply

dependent on cirrhosis [7]. Corticosteroids could attenuate the inflammatory reaction that promotes liver injury and malignant transformation, on a background of cirrhosis. Are corticosteroid treatment protective or deleterious? [4,7]. HCC seemed to need more time to develop in patients with corticosteroid therapy (12.4 years) than in patients without corticosteroids (5.0 years). This observation suggested that liver cirrhosis had a greater effect on carcinogenesis in AIH than corticosteroids [26]. At the same time, the prognosis of HCC associated with AIH was found to be very poor [26].

In AIH patients HCC developed in the same proportion in females and in males, although AIH predominated in females [5,7]. This aspect suggested the intervention of other risk factors for HCC, apart of the AIH context.

A comparison with other autoimmune liver diseases demonstrated a similarly increased risk for hepatobiliary cancers for AIH and primary biliary cirrhosis (PBC) [10,27], now termed primary biliary cholangitis. In PBC, the 12-month biochemical non-response represented the most significant risk factor for future development of HCC [28].

Extrahepatic malignancies in patients with autoimmune hepatitis

Extrahepatic cancers have been also recorded in autoimmune hepatitis [5,10,16,29,30]. They may be coincidental, directly associated with the liver disease and treatment, or antecedent diseases that predispose to the development of autoimmune hepatitis [5]. The types of cancers recorded after autoimmune hepatitis include solid and hematological cancers. The cancers registered before AIH diagnosis were mainly hematological diseases, that might have required immune-modifying treatments [5,29].

AIH epidemiology

Many studies have been dedicated to AIH and offered the basis for the synthesis of the actual guidelines to diagnose AIH. They offered also insights in AIH epidemiology, risk factors, pathogenesis, pathology, treatment, indices of prognosis, evolution, complications [29,31-37]. The surveillance for HCC in patients with cirrhosis related to AIH has been included in the actual guidelines [29,34].

Regarding the epidemiology, the more striking evidence seemed to be related to the relative rarity of AIH and the geographical distribution.

Data collected between 2002-2014 suggested an AIH incidence rate of 0.8-3.0/100,000 population, and a prevalence of 11-24/100,000 population [33]. In Europe and America, an incidence of AIH of 0.83-1.9/100 000 population was recorded, and a prevalence of 11.61-42.9/100 000 population. In Asia Pacific region the incidence varied from 0.67 to 2.0, and the prevalence from 4.0 to 24.5, respectively [18]. The average age of AIH patients at accession was around 50 years old (between 32-56 years old in Europe and America, and between 32-60 years old in Asia-Pacific). The female to male ratio varied between 3:1 to 12:1 in Europe and America, and between 3:1 to 19:1 in Asia Pacific [18]. The 10-year survival rate of AIH patients varied between 73.6% to 94% in Europe and America, and between 80% to 94.9% in Asia Pacific [18].

AIH could represent 11-20% of all causes of chronic hepatitis, this being an important information for the clinical practice [36]. The percentage of AIH-induced cirrhosis at accession varied from 24% to 85 % in Europe and America and from 5.4% to 45.5% in Asia-Pacific region [18].

The studies dedicated to the genetic epidemiology of AIH highlighted the genetic predisposition to AIH and its diversity, that varied between countries, but also inside countries, and between different populations [18]. In Europe and America, the dominant HLA profile conferring susceptibility to AIH was found to be HLA-DR3 (DRB1*0301) and HLA-DR4 (DRB1*0401). In Asia, HLA-DR4 was more common than HLA-DR3 [18]. Using a genome-wide association method of study, HLA-DRB1*0301 was identified as a primary susceptibility genotype, and HLA-DRB1*0401 as a secondary susceptibility genotype [38].

AIH etiology

The etiology of AIH is unknown, though both environmental factors and genetics are likely to be involved as triggers of the autoimmune liver disease [29,35,39-46,47]. As a consequence, a systematic screening for possible etiological risk factors/differential diagnosis of AIH should be mandatory in every patient [29].

AIH should be considered as an alternate "emerging' diagnosis in cases with previous viral infections followed by unexplained and prolonged hepatitis. They could include hepatitis viruses, such as hepatitis A (HAV) and E (HEV), but also infections with 'non-hepatitis' viruses, such as Epstein-Barr, human herpes 6, measles [29].

AIH could develop after the administration of drugs, supplements or herbals. Historically, AIH drug-induced has been described in relation to drugs no longer in use. The list of new drugs having hepatic side-effects is increasing. More recently, the treatment with biological agents has been implicated (TNF-α blockade) as well as after interferon-α for HCV infection. Drug-induced AIH is difficult to be differentiated from drug-induced liver injury (DILI) [29]. AIH-like disease was observed after liver transplantation for other liver diseases (de novo AIH) [29].

Concurrent autoimmune or immune mediated diseases could by commonly found in patients with AIH or in first-degree relatives. Therefore, an extended diagnostic screening for other autoimmune diseases seems reasonable in patients with AIH, both at diagnosis and at regular intervals during the follow-up [29].

Screening of patients with AIH-cirrhosis for HCC

A systematic review and meta-analysis was published recently, with the aim to critically evaluate the evidence regarding the risk of HCC in AIH patients, and to appreciate the necessity of HCC screening in patients with AIH cirrhosis [48]. The overall incidence rate of HCC

(estimated as incidence per 1,000 patients-years) was 3.06, higher in patients with cirrhosis at the time of AIH diagnosis (10.07), and lower in AIH patients without cirrhosis (1.14). The large majority of patients with AIH developing HCC had cirrhosis prior to, or at the time of HCC diagnosis. When compared to other etiologies of cirrhosis, the risk of HCC appeared to be lower than the risk associated to HBV and HCV cirrhosis, and PBC. The necessity of HCC surveillance in patients with AIH cirrhosis was emphasized [48].

Our study has several limitations related to the selected studies and the lack of meta-analysis. The studies were selected according to the items that we intended to analyse (number of AIH patients, patients with AIH-related cirrhosis, frequency of AIH-related HCC, duration of follow-up of patients with AIH) in a definite period of time (1989-2016), in patients tested for HBV and HCV.

Conclusions

The occurrence of HCC in patients with AIH appeared to be similar before and after the discovery of HCV, and was mainly associated with the presence of cirrhosis. An interesting issue could be to find which are the intervening risk factors that completed this 'etiological gap'.

The other aspects revealed by the present literature review confirmed the previous known ascertainements about AIH-related HCC, like the relation with cirrhosis, the long time of evolution of AIH towards cirrhosis and eventually to HCC, and the relatively rare development of HCC in the context of AIH. Surveillance of patients with AIH-related cirrhosis for HCC should be mandatory. The incidence of AIH is apparently low, but its prevalence could be not negligible in relation to the development of complications, such of cirrhosis and HCC.

Further research is required to survey the occurrence of HCC in AIH patients, and the relation with the other etiologies/determinants of AIH, cirrhosis and HCC.

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