Clinical characteristics of hepatocellular carcinoma in patients with cirrhosis: a comparative cohort study

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Abstract

Background and study aims: **The epidemiology of cirrhosis has changed over the last two decades. We aimed to assess whether the epidemiology and clinical presentation of hepatocellular carcinoma (HCC) occurring in cirrhosis has changed .**

Patients and methods: **The patients were recruited from the Cirrhosis Registry. This database included patients with cirrhosis who had attended the outpatient' liver clinic at the Centre Hospitalier Jolimont in La Louvière, Belgium, since January 1995. We extracted data on two cohorts of patients with cirrhosis collected over an identical time period and followed up for the same duration.**

Results: **Cohort 1 included 504 patients enrolled from 1995 to 2005; among them, 89 patients developed HCC during the defined follow-up period (group 1). Cohort 2 included 566 patients enrolled from 2006 to 2016, among whom 73 patients developed HCC during the defined follow-up period (group 2). When patients with HCC in both groups were compared, no differences were found in the age at HCC diagnosis, the test that alerted on the presence of HCC, the extension, and the stage of the lesion at diagnosis. In the group 1, hepatitis C virus-related HCC occurred in 53% of the cases compared with 18% in the group 2 (P<0.001). Alcohol-related HCC occurred in 27% in the group 1 compared with 60% in the group 2 (P<0.001). The prevalence of metabolic dysfunction-associated steatotic liver disease-related HCC accounted for 10% in all groups.**

Conclusion: **The general epidemiology of HCC has not changed; however the etiology of underlying cirrhosis has changed.** (Acta gastroenterol. belg., **2023,** 86, **412-416**).

Keywords: Hepatocellular carcinoma, cirrhosis, epidemiology.

Introduction

The epidemiology of cirrhosis has changed over the last two decades namely metabolic dysfunction-associated steatotic liver disease (MASLD) is an emerging cause of cirrhosis while hepatitis C virus-related cirrhosis has decreased over time (1,2). This study aimed to assess whether the epidemiology and clinical presentation of hepatocellular carcinoma (HCC) occurring in cirrhosis has also changed over the last 25 years.

Methods

Patients with HCC were recruited from the Cirrhosis Registry. This database has been discussed elsewhere (1,3) and included all patients with cirrhosis who had attended the outpatient' liver clinic at the *Centre Hospitalier Jolimont* since January 1995. The *Centre Hospitalier Jolimont* is located in La Louvière, a working-class city with 80,000 inhabitants in the central part of Belgium. The Cirrhosis Registry was initially designed to better understand the epidemiology of cirrhosis and improve surveillance for HCC. Therefore, general data (such as date of inclusion, date of cirrhosis diagnosis, age, sex, etiology of cirrhosis, history of ascites, Child-Pugh score, alpha-fetoprotein level, ultrasonography findings) were prospectively collected.

The diagnosis of cirrhosis was based on histology and/or on clinical, laboratory of imaging evidences as currently accepted (4,5). The etiology of cirrhosis was determined at the time of inclusion in the registry. When several risk factors for cirrhosis were present, the most evident cause was chosen. Rarely, the etiology of cirrhosis was changed during the follow-up. All stages of cirrhosis were included regardless of severity.

Patients underwent follow-up at least every 6 months with blood tests and liver ultrasonography, and more often if required by their clinical condition. Information about patients lost to follow-up was regularly obtained through the electronic medical records of the hospital and/or phone calls to the patient, his family, and eventually, the general practitioner.

From this registry, we extracted data on two cohorts of patients with cirrhosis collected over an identical time period (11 years) but 11 years apart and followed up for the same duration. Cohort 1 included patients with cirrhosis enrolled in the registry from 1995 to 2005, and follow-up of this cohort was censored in 2009. Cohort 2 included patients enrolled from 2006 to 2016, and follow-up of this cohort was censored in 2020. Accordingly, in both cohorts, the first and last included patients were followed up for 15 and 4 years, respectively.

The patients who developed HCC during the defined follow-up period in both cohorts were selected and compared. The diagnosis of HCC was based on histology, typical characteristics on medical imaging, and clinical evolution. HCC was considered as "incident" when not present at the time of inclusion in the registry and "concomitant" if present at inclusion or within the following 6 months.

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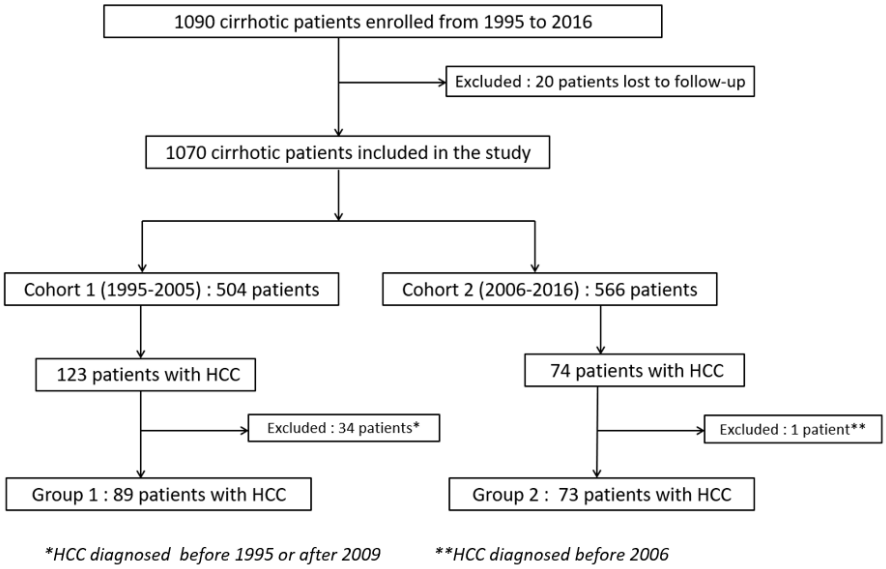

Figure 1. — Flow chart

Table 1. — **Epidemiological characteristics of patients with cirrhosis in both cohorts**

	Cohort 1 (1995-2005) N = 504	Cohort 2 (2006-2016) N = 566	*P*
Sex (male) (%)	316 (63%)	363 (64%)	*ns*
Mean age at diagnosis of cirrhosis (years)	56 ± 13	59 ± 12	*ns*
Mean age at inclusion (years)	58 ± 13	60 ± 11	*ns*
Mean Child Pugh score at inclusion	6,4 ± 2,1	6,4 ± 2	*ns*
Etiology of the underlying cirrhosis			
Alcohol	285 (56,5%)	364 (64%)	*0.009*
HCV	132 (26%)	76 (13%)	*<0.001*
MASLD	34 (7%)	78 (14%)	*<0.001*
Other*	53 (10,5%)	48 (8%)	*ns*

HCV : hepatitis C virus. MASLD : Metabolic dysfunction-associated steatotic liver disease. *Other etiology of cirrhosis in the cohort 1: hepatitis B virus (n=21), autoimmune hepatitis (n=14), hereditary hemochromatosis (n=11), drug-induced liver injury (n=5), secondary hemochromatosis (n=1), cirrhosis of unknown etiology (n=1). Other etiology of cirrhosis in the cohort 2 : hepatitis B virus (n=15), autoimmune hepatitis (n=14), cirrhosis of unknown etiology (n=3), drug-induced liver injury (n=4), hereditary hemochromatosis (n=3), primary biliary cholangitis (n=4), hepatitis delta virus (n=1), secondary hemochromatosis (n=1), cardiac cirrhosis (n=2), Wilson's disease (n=1). NS : non significant.

Informed consent was not required when the Cirrhosis Registry was initiated. However, all patients were aware of their inclusion in the registry and gave their consent verbally. This study was approved by the ethics committee of our institution.

Statistical analyses

Analyses were performed using Microsoft Excel. Differences between the groups were compared using the chi-square test for categorical variables and Student's t-test for continuous variables. Statistical significance was set at $P < 0.05$.

Results

From January 1995 to December 2016, 1,090 patients with cirrhosis were included in the registry. Among them, 20 were excluded because they were lost to follow-up. In the remaining 1,070 patients, the main cause of cirrhosis was alcohol abuse in 649 patients (61%), hepatitis C virus (HCV) infection in 208 patients (19%), metabolic dysfunction-associated steatotic liver disease (MASLD) in 112 patients (10%), and other causes in 101 patients (9%). These 1,070 patients were separated into two cohorts whose data were collected 11 years apart: cohort 1 included 504 patients enrolled from 1995 to 2005, and cohort 2 included 566 patients enrolled from 2006 to 2016. Of the 504 patients with cirrhosis in cohort 1, 123 developed HCC. Among these 123 patients, 34 were excluded because HCC occurred before inclusion in the registry or after the defined follow-up period. The remaining 89 patients belonged to group 1. Of the 566 patients with cirrhosis in cohort 2, 73 developed HCC during the defined follow-up period. These patients belonged to group 2 (Fig. 1).

Epidemiological characteristics of cirrhosis in both cohorts

When compared to each other, both cohorts of patients with cirrhosis were similar in terms of age, sex and Child-Pugh score at inclusion in the registry. In contrast, both cohorts differed in terms of etiology of cirrhosis. In the first and second cohorts, alcohol-related cirrhosis accounted for 57% and 64% (P=0.009), HCV-related cirrhosis accounted for 26% and 13% (P< 0.001) and MASLD-related cirrhosis accounted for 7% and 14% (P< 0.001), respectively (Table 1).

Incidence of HCC during the defined follow-up period

Table 2 reports the proportion of patients with cirrhosis who developed HCC according to the cirrhosis etiology in the two cohorts and during the defined follow-up period. We noted a decline in the incidence of HCC in HCV-related cirrhosis and in MASLD-related cirrhosis, and an increase in HCC in alcohol-related cirrhosis (Table 2).

Table 2. — **Incidence of HCC during the defined follow-up period**

Etiology of HCC	Cohort 1 (1995-2005) N = 504	Cohort 2 (2006-2016) N = 566	*P*
Alcohol	24/285 (8%)	44/364 (12%)	*ns*
HCV	47/132 (36%)	13/76 (17%)	*0.004*
MASLD	9/34 (26%)	8/78 (10%)	*0.03*
Other	9/53 (17%)	8/48 (17%)	*ns*

What has not changed between patients with HCC in both groups

Among the 89 patients with HCC in group 1, HCC diagnosis was concomitant with cirrhosis diagnosis in 26 cases (29%), similar to 22 cases (30%) among 73 patients with HCC in group 2**.** Accordingly, patients with HCC diagnosed concomitantly with cirrhosis were excluded from the surveillance program.

When patients with HCC were compared between the two groups (Table 3), no differences were found in the age at HCC diagnosis, the test that indicated the presence of HCC, and the extension and stage of the lesion at diagnosis. Moreover, there were no differences in the proportion of HCC discovered inside and outside the surveillance program. Remarkably, alpha-fetoprotein was the only alerting test in 15 % and 9,5 % of the cases in the first and second groups, respectively.

What has changed between patients with HCC in both groups

The main change during the last 25 years was the etiology of underlying cirrhosis (Table 4). In group 1, HCV-related HCC occurred in more than half of the cases (53%) whereas in group 2, alcohol-related HCC occurred in 60% of the cases. In contrast, the prevalence of MASLD-related HCC was not different between the groups and was approximatively 10%.

Discussion

The aim of this study was to assess changes in the characteristics of HCC in our region over a 25-year period. To achieve this goal, we compared the epidemiology and presentation of HCC occurring in two cohorts of patients with cirrhosis collected consecutively during an equivalent period of time but 11 years apart and followed up for the same duration (see Methods). Both cohorts with cirrhosis were similar in terms of epidemiological characteristics such as sex, age, and severity of cirrhosis according to the Child-Pugh score, but differed according to the cause of cirrhosis. As previously reported, the prevalence of HCV-related cirrhosis decreased whereas the prevalence of MASLD-related cirrhosis increased in our region (1). According to the defined follow-up period, 89 patients in the first cohort (HCC group 1) and 73 in the second cohort (HCC group 2) developed HCC.

Table 3. — **Comparison between patients with HCC in both groups … What has not changed**

	HCC group 1 N = 89 HCC (Cohort 1995-2005)	HCC group 2 N = 73 HCC (Cohort 2006-2016)	*P*
Sex (male) (%)	59 (66%)	58 (79%)	*ns*
Mean age at diagnosis of HCC	68 ± 9	67 ± 11	*ns*
Mean Child Pugh score at diagnosis of HCC	6,4 ± 1,9	6,1 ± 1,8	*ns*
Incident HCC	63 (70,5%)	51 (70%)	*ns*
Concomitant HCC	26 (29%)	22 (30%)	*ns*
HCC diagnosed under surveillance	45 (50,5%)	38 (52%)	*ns*
Alerting test: US/AFP/US+AFP/Other	41,5% / 15% / 40% / 4,5%	57,5% / 9,5%/ 22% / 11%	*ns*
Isolated nodule ≤3 cm	33 (37%)	32 (44%)	*ns*
Diffusely-infiltrating HCC	25 (28%)	13 (18%)	*ns*
Milan-in criteria	56 (63%)	45 (62%)	*ns*
BCLC staging (0/A versus C/D)	46% versus 41,5%	52,5% versus 28%	*ns*

Table 4. — **Comparison between patients with HCC in both groups … What has changed**

Etiology	HCC-Group 1 N = 89 HCC (Cohort 1995-2005)	HCC-Group 2 N = 73 HCC (Cohort 2006-2016)	P
Alcohol	24 (27%)	44 (60%)	<0.001
HCV	47 (53%)	13 (18%)	<0.001
MASLD	9 (10%)	9 (12%)	ns
Other*	9 (10%)	7 (10%)	ns

*Other etiology of HCC in the HCC-group 1 : hepatitis B virus (n=6), hereditary hemochromatosis (n=2), autoimmune hepatitis (n=1); Other etiology of HCC in the HCC-group 2 : hepatitis B virus (n=4), hereditary hemochromatosis (n=2), autoimmune hepatitis (n=1); Ns : non significant.

The current study shows that many characteristics of HCC have not changed in our region over the last 25 years. The epidemiology of HCC did not differ between the two periods in terms of sex, age, and the Child-Pugh score at diagnosis. The presentation of HCC at the time of diagnosis was also similar between the two periods. There were no differences in the size and extension of the lesion (imaging, Milan criteria in/out) or Barcelona Clinic Liver Cancer (BCLC) stage between the two HCC groups. This may be explained by the fact that we began a surveillance program for HCC in patients with cirrhosis in 1995. Indeed, the emergence of HCC treatment by percutaneous injection of alcohol or acetic acid in the early 90s regained our enthusiasm for HCC surveillance in patients with cirrhosis (6). Therefore, we strongly encouraged patients to participate in the surveillance program at the beginning of the Cirrhosis Registry in January 1995. Accordingly, the proportion of HCC discovered under surveillance was identical for both periods (approximatively 50%, Supplementary Table 1). In addition, the tests indicating the presence of HCC (alpha-fetoprotein, ultrasonography, or other imaging techniques) were similar between both periods. Interestingly, the break in the alpha-fetoprotein curve, while ultrasonography was reported as negative, was the only indicator of the presence of HCC in 12% of the cases. Currently, the use of alpha-fetoprotein for the surveillance of HCC emergence in cirrhosis is generally considered to be of little or no interest (7,8); however, in our opinion, it remains a useful tool.

The main findings that must be highlighted between both groups of HCC are related to the etiology of underlying cirrhosis.

First, the prevalence of HCV-related HCC decreased over time from 53 to 18%. However, this decrease was not expected to occur so early in Belgium. Belgian projections made in 2013 estimated an increase in the number of HCV cirrhosis cases by 2030 (9). This unexpected decrease in the prevalence of HCV-related HCC may be due to at least two main reasons. One reason for this might be an overestimation of the number of HCV-infected patients in Belgium. Sciensano (the Belgian Institute of Public Health) recently reported that HCV seroprevalence in Belgium was much lower than that previously estimated (10). Another reason might be the emergence of a very effective treatment for HCV infections. Indeed, the direct-acting antiviral agents have been considered one of the main advances in the field of medicine in recent years (11) and the WHO target is to reach elimination of HCV infection in high-income countries for 2030 (12).

Second, the prevalence of alcohol-related HCC increased during the most recent period from 27 to 60%. Of course, this increase is largely explained by the decrease of the HCV-related HCC, but this is not the only factor. Indeed, we observed an increase in the number of alcohol-related HCC and an increase of the proportion of alcohol-related cirrhosis developing HCC. We have no definitive explanation for these findings. A possible explanation could be the increase in alcohol consumption in Belgium. According to Sciensano, alcohol consumption in Belgium peaked between 2000 and 2005 (13). Another possible explanation could be the emergence of MASLD. Alcohol- and MASLD-related liver injuries are intricate. Patients with metabolic syndrome may be more susceptible to the deleterious effects of alcohol. According to a recent review, patients with abdominal obesity could have a fourfold increase in alcohol-related toxicity (14).

Third, the prevalence of MASLD-related HCC did not changed between the periods. Indeed, even though the prevalence of MASLD-related cirrhosis has doubled in the more recent cohort with cirrhosis, this has no repercussion on the prevalence of MASLD-related HCC in both groups (10% for the first period and 12% for the more recent period). Moreover, the proportion of MASLD-related cirrhosis developing into HCC has significantly decreased from 26% during the first period to 10% during the most recent period. We have no clear explanation, but the paradoxical absence of an increase in MASLD-related HCC despite the increase in MASLD-related cirrhosis has been reported in another study (15). It could be explained by the fact that the MASLD epidemic is recent and results in an increasing burden of chronic liver disease, but has not yet resulted in a large increase in HCC burden, which is expected at approximatively 2030 (15). Moreover, because liver injury in MASLD is slowly progressive and because the first causes of death in these patients are malignancies and cardiovascular diseases, it may be presumed that these patients died before developing HCC (16). In light of this, it could be noted that the median age of our patients with MASLD-related HCC was particularly elevated at 73.8 years.

Another interesting point is that compliance to the surveillance program resulted, as expected, in the discovery of HCC at an earlier stage of cirrhosis according to the Child-Pugh score, less extensive lesions on medical imaging and better prognostic stage according to the BCLC staging (Supplementary Tabl 2). In our opinion, the observance of the surveillance program was well-respected. Among the 114 cases of incident

Supplementary Table 1. — **Adherence to the surveillance program according to the HCC groups**

Surveillance	All HCC (group 1 and 2) N = 162 (Cohort 1995-2016)	HCC group 1 N = 89 HCC (Cohort 1995-2005)	HCC group 2 N = 73 HCC (Cohort 2006-2016)	*P*
HCC diagnosed within surveillance	83 (51%)	45 (50,5%)	38 (52%)	*ns*
HCC diagnosed outside surveillance*	23 (14%)	13 (15%)	10 (14%)	*ns*
HCC concomitant at cirrhosis diagnosis**	56 (34,5%)	31 (35%)	25 (34%)	*ns*

* HCC diagnosed after stopping surveillance; **HCC concomitant at cirrhosis diagnosis or within the following 6 months.

Supplementary Table 2. — **Comparison between patients with HCC diagnosed within and outside the surveillance program**

	All HCC (group 1 and 2) N = 162 (Cohort 1995-2016)	HCC diagnosed within surveillance N = 83	HCC diagnosed outside surveillance* N = 79	*P*
Sex (male) (%)	117 (72%)	60 (72%)	57 (72%)	*ns*
Mean age at HCC diagnosis (years)	67,4 ± 10	66,4 ± 10,2	68,4 ± 9,6	*ns*
Child Pugh score A at HCC diagnosis	108 (67%)	63 (76%)	45 (57%)	*0,01*
Child Pugh score B at HCC diagnosis	34 (21%)	13 (16%)	21 (26,5%)	*ns*
Child Pugh score C at HCC diagnosis	20 (12%)	7 (8%)	13 (16,5%)	*ns*
Isolated nodule ≤3 cm	65 (40%)	57 (69%)	8 (11%)	*<0.001*
Diffusely-infiltrating HCC	52 (32%)	6 (7%)	46 (58%)	*<0.001*
Milan-in criteria	102 (63%)	77 (93%)	25 (32%)	*<0.001*
BCLC staging : 0/A	79 (49%)	60 (72%)	19 (24%)	*<0.001*
BCLC staging : B/C/D	83 (51%)	23 (28%)	60 (76%)	*<0.001*

** HCC diagnosed outside surveillance included : patients who stopped surveillance (n=23) and patients with HCC concomitant at cirrhosis diagnosis or within the following 6 months (n=56).

HCC, 83 (73%) were discovered under the surveillance and this figure did not differ between the two groups with HCC nor the etiology of the underlying cirrhosis. The same proportion of HCC (50%) was discovered under surveillance, and the same proportion of patients abandoned the surveillance regardless of the etiology of cirrhosis (alcoholic or viral).

Finally, the key lesson of the current study is that the diagnosis of cirrhosis and HCC was concomitant in 34% of all patients with HCC (56/162 cases, Supplementary Table 1). Accordingly, we must diagnose cirrhosis before diagnosing HCC. Nowadays, this has become easier with the emergence of non-invasive methods to assess liver fibrosis.

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