The changing pattern of cirrhosis in Belgium : a study based on two cohorts prospectively collected 15 years apart

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Abstract

***Background and study aim* : The epidemiology of cirrhosis is evolving over the past decades in Western countries. The aim of this study was to assess the changes in the epidemiology of cirrhosis in our region by comparing two cohorts of patients diagnosed 15 years apart.**

***Patients and methods* : From the outpatient's liver clinics of our hospital and from January 1995 to December 2017, we consecutively recorded all patients with cirrhosis. From this registry, the current study compared two cohorts of patients diagnosed 15 years apart. Epidemiologic data and liver-related mortality were compared between both cohorts with a 3 to 8-year follow-up.**

***Results* : During a 23-year period, 1151 patients consented to be included in the cirrhosis registry. The current study compared 197 patients with cirrhosis diagnosed from 1995 to 1999 (cohort C1) with 237 patients with cirrhosis diagnosed from 2010 to 2014 (cohort C2). Our results showed that in the cohort C2, compared with the cohort C1, the prevalence of NAFLD-related cirrhosis increased (C1 : 3% vs C2 : 16%, p< 0.0001) while the prevalence of HCV-related cirrhosis decreased (C1 : 22% vs C2 : 10%, p< 0.0001). In the more recent cohort, liver biopsy was less frequently performed (C1 : 65% vs C2 : 20%, p<0.0001). An intriguing finding was the increasing age at cirrhosis diagnosis for patients with alcohol-related cirrhosis (C1 : 52±11 years vs C2 : 57±10 years, p<0.0001).**

***Conclusions* : The epidemiology of cirrhosis has changed over time. Effective prevention strategies are needed to reduce the burden of liver disease.** (Acta gastroenterol. belg., **2020**, 83, **559-563**).

Key words : epidemiology, cirrhosis, cohort study

Introduction

In Western countries, the main causes of cirrhosis include excessive alcohol consumption, hepatitis C virus (HCV) infection and nonalcoholic fatty liver disease. The epidemiology of cirrhosis has changed over the past decades. First, the burden of HCV infection is declining. Indeed, the transmission of the virus has largely decreased due to routine screening for HCV in blood donners and to observance of preventive measures against HCV transmission (1-2). Moreover, thanks to the development of therapy for HCV, viral eradication has been associated with a decline in liver-related complications and liver-related death (3-8). Recent studies recommend screening campaigns for HCV infection (9-11).

Secondly, attention has shifted to nonalcoholic fatty liver disease (NAFLD) which has emerged as an increasing cause of cirrhosis concomitantly with the increasing prevalence of obesity and type 2 diabetes (12-14).

The aim of this study was to describe the changes in the epidemiology of cirrhosis in our region by comparing 5-year characteristics and 8-year outcomes in two cohorts of patients diagnosed 15 years apart.

Patients and methods

From January 1995 to December 2017, all patients referred to the outpatient's liver clinics by one of us at the Jolimont Hospital were consecutively enrolled in a registry if they fulfilled the following criteria : (1) age >18 years, (2) cirrhosis demonstrated by liver biopsy showing fibrotic nodules consistent with a METAVIR F4 fibrosis stage or by unequivocal signs of cirrhosis (dysmorphic liver, ascites, esophageal or gastric varices). From 2006, we had the possibility to perform transient elastography by FibroScan^{R} of first generation (Echosens, Paris, France). Nevertheless, in the absence of histological confirmation, the diagnosis of cirrhosis was never accepted without an evident cause of chronic liver disease and unequivocal signs of cirrhosis. All stages of cirrhosis were included and 1151 patients were included in the registry. The main etiology of cirrhosis was determined at the time of the inclusion following history, clinical, biological or serological findings. NAFLD-related cirrhosis was determined on the criteria of the metabolic syndrome when other causes were excluded.

When several risk factors may play a role in the etiology, the most evident cause was chosen. During follow-up, patients were seen as outpatients every 6 months according to standard care of such disease, or more frequently if required. Data related to the development of hepatocellular carcinoma, the occurrence of liver transplantation or death were collected. Examination by Doppler ultrasonography was performed every 6 months for hepatocellular carcinoma surveillance. When this registry began, written informed consent and ethical committee approval were not mandatory. However, patients were informed about their participation to an observational registry as soon as it became a rule for an

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observational study to ask patient's consent and patients gave informed consent verbally.

From this registry collected during a 23-year period, we chose to compare two periods of 5 years separated by 15 years. Accordingly, we extracted two cohorts of patients according to the known date of diagnosis of cirrhosis. The cohort C1 (C1) included patients in whom diagnosis of cirrhosis was made between 1995 and 1999. The cohort C2 (C2) included patients diagnosed from 2010 to 2014. We compared baseline characteristics and liver-related deaths (deaths due to hepatocellular carcinoma or decompensation of cirrhosis) between both cohorts for the leading etiologies (alcohol, HCV and NAFLD-related cirrhosis) with a 3 to 8-year follow-up (end of 2002 for the cohort C1 and end of 2017 for the cohort C2). When the patients were no longer followed at the outpatients' liver clinics, the medical records of the hospital were consulted and, in case of lack of information, the general practitioner and/or the patient himself were contacted. The last data were collected in April 2018.

Statistical analysis

Analyses were conducted using the chi-square test for categorical variables and Student's t-test for continuous variables. Follow-up started at the inclusion of patients. A p-value <0.05 was considered significant.

Results

From the whole cirrhosis registry including 1151 patients over a 23-year period, we selected 205 patients with cirrhosis diagnosed from 1995 to 1999 (cohort C1) and 240 patients with cirrhosis diagnosed from 2010 to 2014 (cohort C2). From those patients, 8 from the first period and 3 from the second period were excluded because no information could be found about survival and medical follow-up. Accordingly, the cohort C1 included 197 patients and the cohort C2 included 237 patients.

The main etiology of cirrhosis according to the time period of diagnosis is shown in Table 1. In the cohort C2, compared with the cohort C1, the prevalence of HCV-related cirrhosis decreased from 22% to 10% (p< 0.0001), while the prevalence of NAFLD-related cirrhosis increased from 3% in the cohort C1 to 16% in the cohort C2 (p<0.0001). The prevalence of alcohol-related cirrhosis remained similar between both cohorts.

Table 1. — **Main etiologies of cirrhosis**

	Cohort C1 (1995-1999) N = 197	**Cohort C2 (2010-2014) N = 237**	*p*
Alcohol	128 (65%)	159 (67%)	*0.6*
HCV	43 (22%)	23 (10%)	*< 0.0001*
NAFLD	6 (3%)	37 (16%)	*< 0.0001*
HBV	11 (6%)	3 (1%)	*0.01*
Autoimmune	3 (2%)	11 (5%)	*0.07*
Other*	6 (3%)	4 (2%)	*0.3*

HCV, hepatitis C virus ; NAFLD, nonalcoholic fatty liver disease ; HBV, hepatitis B virus. * Cohort C1 : Hereditary hemochromatosis (n=4), secondary hemochromatosis (n=1), drug-induced liver injury (n=1). *Cohort C2 : Hereditary hemochromatosis (n=1), drug-induced liver injury (n=1), cirrhosis of unknown etiology (n=2).

For alcohol-related cirrhosis (Table 2), the sex ratio remained stable between both cohorts, but ages at the time of cirrhosis diagnosis were on average significantly higher (p<0.0001) in the cohort C2 (57±10 years) than in the cohort C1 (52±11 years). The severity of alcohol-related cirrhosis assessed by Child-Pugh score at inclusion in the registry was not significantly different between both cohorts as well as liver-related mortality and non-liver-related mortality. However, mean age at liver-related death was significantly higher (p=0.004) in the cohort C2 (62±9 years) compared to cohort C1 (57±12).

For HCV-related cirrhosis (Table 3), both cohorts exhibited comparable rates of sex, age at cirrhosis diagnosis and severity of cirrhosis. However, the mean age at liver-related death was significantly higher (p=0.003) in the cohort C2 (82±3 years) compared to cohort C1 (70±6 years). Liver-related death was almost significantly higher in the cohort C1 than in the cohort C2 (p=0.06).

Concerning NAFLD-related cirrhosis (Table 4), there were no statistical differences between both cohorts. In this group of patients, comparisons are not reliable due to the small sample of patients in the cohort C1.

Table 2. — **Alcohol-related cirrhosis**

	Cohort C1 (1995-1999) N = 128	**Cohort C2 (2010-2014) N = 159**	*p*
Sex (M)	88 (69%)	115 (72%)	*0.5*
Mean age (years)	52 ± 11	57 ± 10	*< 0.0001*
Child-Pugh score A B C	 43% 39% 18%	 51% 31% 18 %	 *0.2* *0.2* *0.9*
Liver-related mortality	40 (31%)	39 (25%)	*0.2*
Mean age at liver-related death (years)	57 ±12	62 ± 9	*0.004*
Non-liver-related mortality	12 (9%)	18 (11%)	*0.6*
Mean age at non-liver-related-death (years)	56 ± 12	63 ± 12	*0.2*

Table 3. — **HCV-related cirrhosis**

	Cohort C1 (1995-1999) N = 43	**Cohort C2 (2010-2014) N = 23**	*p*
Sex (M)	21 (49%)	10 (43%)	*0.7*
Mean age (years)	64 ± 10	68 ± 15	*0.3*
Child-Pugh score A B C	 84% 16% 0%	 91% 9% 0%	 *0.4* *0.4* -
Liver-related mortality	12 (28%)	2 (9 %)	*0.06*
Mean age at liver-related death (years)	70 ± 6	82 ± 3	*0.003*
Non-liver-related mortality	4 (9%)	2 (9%)	*0.9*
Mean age at non-liver-related death (years)	73 ± 5,7	81 ± 10	*0.3*

HCV, hepatitis C virus.

Table 4. — **NAFLD-related cirrhosis**

	Cohort C1 1995-1999 N = 6	**Cohort C2 2010-2014 N = 37**	*p*
Sex (M)	2 (33%)	23 (62%)	*0.2*
Mean age (years)	68 ± 10	68 ± 10	*0.1*
Child-Pugh score A B C	 100% 0% 0%	 86% 13% 0%	 *0.3* *0.3* -
Liver-related mortality	2 (33%)	6 (16 %)	*0.3*
Mean age at liver-related death (years)	75 ± 6	67 ± 15	*0.5*
Non-liver-related mortality	1 (17%)	3 (8%)	0.5
Mean age at non-liver-related death (years)	-	72 ± 5	-
Liver biopsy	4 (67%)	17 (46%)	*0.3*

NAFLD, nonalcoholic fatty liver disease

Table 5. — **Liver biopsy**

	Cohort C1 1995-1999 N=197	**Cohort C2 2010-2014 N= 237**	*p*
Liver biopsy	127 (65%)	47 (20%)	*< 0.0001*

Liver biopsy (Table 5) was significantly less frequently performed ($p<0.0001$) in the cohort C2 (20%) than in the cohort C1 (65%).

As reported in the chapter *Patients and Methods*, we had the possibility to perform transient elastography (FibroScan^{R}) from 2006. Transient elastography was never considered as the only criteria for diagnosis of cirrhosis, but was just used as an additional point to confirm the diagnosis in 151 cases of the more recent cohort (cohort C2). Median values (range) were 49,6 (12,1-75) KPa in 94 alcoholic cirrhosis, 21,3 (10,4-54,2) KPa in 19 HCV-related cirrhosis and 29,1 (12,6-75) in 23 NASH-related cirrhosis.

Discussion

The aim of this study was mainly to assess the epidemiologic changes of cirrhosis in our region by comparing two cohorts of patients with cirrhosis diagnosed 15 years apart. This comparison has evident limitations but also some strengths. The most important limitation is that our cirrhosis registry was not designed, at origin, for this current comparison. Even if the enrolment of patients' and the data collection were prospective, the cirrhosis registry was mainly designed to assess the incidence and improve the surveillance of hepatocellular carcinoma. This explains why many interesting epidemiological data were not recorded. Unfortunately, it is nowadays impossible to recover supplementary data because patient's files before the year 2000 are no longer available in our center. A second limitation is that the Child-Pugh score was calculated at the inclusion into the registry during a visit at the outpatients'liver clinics and not systematically at the time of cirrhosis diagnosis. In the majority of cases, the date of cirrhosis diagnosis and the date of enrolment into the registry were concomitant. In some cases, however, the patients were included with some delay (generally less than one month) after a hospital stay for complications of cirrhosis and, in those cases, the health status and the Child-Pugh score could have been improved. In spite of these limitations, this comparison study has some strengths. The most important is the homogeneity of this study. It is a monocentric study and the patients were consecutively and exhaustively included at the outpatient's liver clinics by one of us according to accepted criteria in the literature (15-17)

Moreover, we made all efforts to record the follow-up of patients who were not longer seen at the outpatient's

liver clinics. Accordingly, only 11 of 445 patients (2.5%) were totally lost for follow-up.

Some interesting observations may be raised from this comparison between two cohorts of cirrhosis diagnosed 15 years apart. Our results are consistent with other studies showing that NAFLD is an emerging cause of cirrhosis (18) and that liver biopsy tended to disappear following the development of non-invasive methods of liver fibrosis assessment (Table 5) (19).

Our study showed a lower liver biopsy rate for the diagnosis of cirrhosis in the cohort C2 than in the cohort C1. In fact, even though the liver biopsy is considered as the gold standard for the diagnosis of cirrhosis, it is now recognized in literature that a diagnosis of cirrhosis can be made based on clinical, laboratory and imaging findings (15-17). In the cohort C2 (2010-2014) we had the opportunity to use transient elastography. The results largely confirmed the diagnosis of cirrhosis and validated our clinical, laboratory and imaging criteria for the diagnosis of cirrhosis. Even if we never accepted the diagnosis of cirrhosis only on the basis of transient elastography, it is evident that nowadays, the emergence of non-invasive methods to assess hepatic fibrosis, as well as the impressive progresses in liver imaging .largely explains why liver biopsy is far less frequently performed.

We also observed that the prevalence of HCV-related cirrhosis is already decreasing. This was not really expected. Indeed, recently, forecasting models showed that the prevalence of HCV-related cirrhosis will increase in Belgium until the year 2030 (20-22). Probably, the very effective treatment with direct acting antiviral agents has stopped the progression of the disease. The emergence of this effective treatment and also the progress in the management of patients with decompensated cirrhosis explain probably why patients with HCV-related cirrhosis died later of liver disease.

Finally, the most intriguing observation raised from the current comparison, is the increasing age at the time of cirrhosis diagnosis in patients with alcohol-related cirrhosis. In the cohort C1, the mean age at cirrhosis diagnosis was 52 years while it was 57 years in the cohort C2 (Table 2). In our opinion, this significant increase in age cannot be explained by an increased delay in cirrhosis diagnosis. Indeed, by comparison with the early 1990, the current general population is more prone to perform regular health evaluation. For example, a yearly systematic blood test is nowadays a current practice. If the increasing age of patients with alcohol-related cirrhosis is not due to delay in diagnosis, it is therefore due to a delay in cirrhosis development in patients who drink alcohol. This delay could be explained by routine blood tests that warn the patients about alcoholic liver injury. At the liver outpatient's liver clinics, it is our daily experience that patients who are drinking too much, come for advice following a blood testing. Another explanation could be that the general population is nowadays better informed about the risk of alcohol consumption and this is an encouraging point for the public health campaign. Moreover, policy interventions (such alcohol tax or increasing the minimum legal drinking age) could play a pivotal role to prevent people from drinking. The same reasons might explain the older age at liver-related death for patients with alcoholic cirrhosis in the second cohort.

In conclusion, our study confirms that the epidemiology of cirrhosis has changed over time. Effective prevention strategies that target liver disease risk factors are needed to reduce the burden of liver disease.

Conflict of interest

The authors declare no conflict of interest

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