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BRIEF REPORT

Late Presentation for Care Among Patients With Chronic Hepatitis C: Prevalence and Risk Factors

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Patients with chronic hepatitis C may have advanced fibrosis at first evaluation. Using the European Association for the Study of the Liver (EASL) definition (FibroScan® >9.5 kPa) for "late presenter for care" (LP), we found that 32% (169 of 527) of patients were LP. Being a LP was associated with increasing age and a history of alcohol overuse.

Keywords. chronic hepatitis C; cirrhosis; fibrosis; late presentation; liver stiffness measurement.

Living with untreated chronic hepatitis C (CHC) may lead to liver cirrhosis, consequently increasing the risk of hepatocellular carcinoma (HCC) and hepatic decompensation [1]. New treatment regimens with directly acting antivirals (DAAs) cure most patients with CHC and reduce the risk of complications, especially if treatment is initiated before advanced fibrosis occurs [2]. Finding the patients at an earlier stage is crucial to achieve the World Health Organization Global Health Sector target of reducing liver-related mortality and morbidity by 65% by 2030 [3]. Patients with CHC may have been infected many years before contact with a treatment facility, and linkage to care has been identified as a major obstacle to receiving treatment and follow-up for liver disease [4].

A definition of "late presentation" has aided the surveillance and identification of risk factors for presenting with advanced human immunodeficiency virus (HIV) at the time of diagnosis [5]. Therefore, the European Association for the Study of the Liver (EASL) and HIV in Europe defined "late presentation for care" (LP) of chronic hepatitis to improve the ability to find patients before they develop advanced fibrosis and improve surveillance within this group as well. Late presentation for care of chronic hepatitis was defined as a liver stiffness measurement (LSM) ≥9.5 kPa, aspartate aminotransferase-to-platelet ratio index score >1.5, FIB-4 >3.25, Fibrotest >0.59, or a biopsy with Metavir score F3 with no previous antiviral treatment. "Presentation with late-stage liver disease" (LSLD) was defined as the presence of HCC or decompensated cirrhosis at first consultation [6]. The purpose of this study was to (1) investigate the prevalence of LP/LSLD at first consultation at a treatment facility in a country with low CHC prevalence and (2) describe associated risk factors.

MATERIAL AND METHODS

This study included all adult (age ≥18 years) CHC patients with a first consultation for CHC at Odense University Hospital, Denmark, from May 2007 to January 2016. Patients were identified through the Danish Database for Hepatitis B and Hepatitis C (DANHEP), a national clinical database including all patients with chronic hepatitis B or CHC admitted to hospitals in Denmark [7]. Missing information was supplemented with data from InfCare, a local quality control database, or extracted from patient records. Liver stiffness measurement was extracted from the FibroScan device (Echosens, France). Data from the different registries were linked using the national, unique 10-digit personal identification number.

Late presentation for care was defined as a reliable LSM ≥9.5 kPa within 180 days of first consultation. Reliability was defined as 10 valid measurements and an interquartile range (IQR)/median <30% if LSM was ≥7.1 kPa [8, 9]. Presenting with LSLD was defined as HCC or decompensation within 180 days of initial consultation.

A history of alcohol overuse was defined as ever having a self-reported use above 3/2 units per day (male/female) for more than 1 year. A history of intravenous drug use (IDU) was defined as ever having a self-reported episode of injecting. The project was approved by The Danish Patient Safety Authority (j.nr 3-3013-2243/1) and the Danish Data Protection Agency (j.nr 2008-58-0035).

Statistical Analysis

Comparison of proportions was done using Pearson's χ^2 test and comparison of median values with Kruskal-Wallis test. Logistic regression models included age groups, sex, origin and history of alcohol overuse, or IDU. There were no statistical significant interactions. Chronic hepatitis B and HIV were excluded in the multivariate models due to small numbers

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using backward elimination. Goodness of fit was examined using the Hosmer and Lemeshow's method with 6 groups. The significance level was set to <0.05. Data were analyzed using STATA, version 14.

RESULTS

From May 2007 to January 2016, 570 patients had a first consultation for CHC. Of the 570 patients, 43 (7.5%) did not have any data available for evaluation of the degree of fibrosis. These patients were a median 4.3 years younger ($P < .005$) and more likely to have a history of alcohol overuse or IDU ($P < .005$) than the included patients.

Late Presentation for Care

There were 169 (32.1%) late presenters for care with no statistically significant change during the 9-year study period. The year 2007 had the highest number of first consultations due to the implementation of a drug center outreach program. Patients with LP were a median of 7 years older than patients with baseline LSM <9.5 kPa ($P < .005$). In univariate analysis, age and a history of alcohol overuse were strongly associated with LP, and this remained significant in multivariable analysis (Table 1).

Presentation With Late Stage Liver Disease

There were 28 (5.3%) patients presenting with LSLD (28 of 169 of the LP patients). Their median LSM was 51.4 kPa (IQR, 25.8–69.1) and median age was 50.9 years (IQR, 45.7–56.1). None of the LSLD patients were under 30 years of age. Among the patients above 30 years of age, a history of IDU was significantly associated with reduced risk of presenting with LSLD (Table 1).

DISCUSSION

In this single-center study including CHC patients in Denmark presenting to specialized care for the first time, we found that 32.1% were LP and 5.3% presented with LSLD. Late presentation for care was associated with increasing age and having a history of alcohol overuse. The exclusion of 43 patients with missing LSM that had indicators associated with less severe disease (young and a history of IDU) could have overestimated the proportion of LP, but even if all the excluded patients had a LSM <9.5 kPa, the percentage of LP would still be 29.6%. In a 5-year follow-up study of CHC, it was shown that LSM >9.5 kPa was associated with significantly higher mortality [10]. This makes the high proportion of LP a significant health problem.

A recently published study from New Zealand reported 17%–22% "late hepatitis notifications", defined as decompensation or HCC before or within 2 years of a reported diagnosis of CHC to the health authorities [11]. Compared with our 5% within 6 months of presentation, their numbers are high. However, the results are difficult to compare because we have no information on whether the patients in the study had a consultation at a treatment facility at the time of diagnosis. The patients in our study may have been infected many years previous to their first contact with care. The time span from infection to testing and from diagnosis and linkage to care is also unknown. Some of the delay in our study may have been due to the limited treatment options of the past, and with the introduction of the highly effective DAA treatment, the delay may be reduced the coming years. It is also likely that the increased screening in asymptomatic patients such as the US baby boomer testing [12] will reduce LP in the near future.

Late presentation for care was associated with increasing age and alcohol overuse, factors that previously have been linked to a high risk of cirrhosis [13, 14]. In our setting, drug users in treatment (opiate substitution therapy) have in the past decade been targeted for hepatitis C virus screening and evaluation for

Table 1. Odds Ratios for Late Presentation for Care and for Having Late-Stage Liver Disease at Initial Consultation

	Model for Late Presentation for Care				Model for Presenting With Late-Stage Liver Disease			
Baseline predictor	Univariate OR |(95% CI)	*P* Value	Multivariate OR (95% CI)	*P* Value	Univariate OR (95% CI)	*P* Value	Multivariate OR (95% CI)	*P* Value
Western European	0.9 (0.5–1.6)	.814	0.8 (0.4–1.5)	.549	0.6 (0.2–1.7)	.384	0.8 (0.2–2.6)	.704
Male sex	1.3 (0.9–1.9)	.211	1.4 (0.9–2.1)	.171	1.2 (0.5–2.7)	.732	1.3 (0.5–3.3)	.563
Age (years)								
<30	1				N/A[a]		N/A[a]	
30–39	3.7 (0.9–16.5)	.081	3.8 (0.9–16.8)	.080	1		1	
40–49	8.9 (2.1–38)	.003	8.6 (2–37.2)	.005	1.9 (0.6–6.4)	.278	1.8 (0.5–5.9)	.352
50–59	17.3 (4–74.8)	<.005	16.5 (3.8–71.9)	<.005	3.8 (1.2–12.1)	.024	3 (0.9–9.8)	.071
60+	15.5 (2.9–81.6)	.001	14.3 (2.7–77)	.002	6.3 (1.3–30.4)	.022	4 (0.8–20.9)	.099
Hepatitis B coinfection	0.8 (0.3–2)	.656	[b]		2.6 (0.7–9.3)	.141	[b]	
HIV[b] coinfection	2.1 (0.4–10.7)	.355	[b]		3.7 (0.4–32.4)	.244	[b]	
History of alcohol use	1.82 (1.2–2.7)	.003	1.7 (1.1–2.7)	.018	2 (0.8–4.7)	.130	2.6 (1–7)	.062
History of intravenous drug use	0.8 (0.4–0.9)	.275	0.8 (0.4–1.4)	.387	0.3 (0.2–0.8)	.008	0.3 (0.1–0.8)	.016

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

[a]No patients in this age group presented with late-stage liver disease.

[b]Coinfection with hepatitis B and HIV was omitted from the multivariate models due to small numbers with insignificant contribution.

liver disease. The examinations have been performed in an outreach setting making linkage to care easy. This is probably the main factor why few patients with IDU were LP in our study.

The association with age was expected but illustrates the missed opportunity to diagnose CHC, especially among former intravenous drug users outside drug treatment centers. None of the patients younger than 30 years of age had LSLD, probably due to infection in their 20s with less time to develop fibrosis. The association of LSLD to not having a history of IDU among the patients above 30 years of age may reflect the higher number of patients acquiring CHC from other sources (primarily nosocomial transmission) in the 1970s and 1980s before hepatitis C screening of blood products were introduced.

CONCLUSIONS

Because a history of IDU accounts for the majority of the Danish CHC population [15], testing for CHC in the population with a former or present IDU remains the most important initiative for earlier diagnosis and timely treatment. However, our data also suggest that screening for CHC and liver disease among persons born before 1970 or with an overuse of alcohol may reduce the risk of LP and presenting with LSLD.

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