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The clinical course of cirrhosis. Population based studies and the need of personalized medicine

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The natural history of cirrhosis is characterised by a silent, asymptomatic course until increasing portal pressure and decreasing liver function result in overt clinical signs. In the asymptomatic phase of the disease, usually referred to as compensated cirrhosis, patients may have good quality of life and the disease may progress undetected for many years. Median survival for compensated cirrhosis has been reported in the range of 10–12 years. The progression of the disease is marked by the development of overt clinical signs, the most frequent of which are ascites, bleeding, encephalopathy, and jaundice. Following the first appearance of any of these signs, the disease has usually a more rapid progression towards death or liver transplant. This more rapid phase of the disease has been designated as "decompensated cirrhosis".

Progression of the decompensated disease may be accelerated by the development of other complications such as (re)bleeding, renal impairment (refractory ascites, hepatorenal syndrome), hepatopulmonary syndrome and sepsis (spontaneous bacterial peritonitis). The development of hepatocellular carcinoma (HCC) may accelerate the course of the disease at any stage. The median survival after decompensation is 2–4 years.

The knowledge of the clinical course of cirrhosis comes mostly from follow-up studies of patient series observed in secondary or tertiary care centres. However, the sample size of these studies has been quite limited [1], while population based studies of cirrhosis are scanty and therefore generalizability of available information on survival of cirrhosis is still uncertain.

In this issue of the Journal a large population based study of cirrhosis is reported from England [2], including a cohort of 5118 patients. The cohort has been assembled using two large electronic databases: the Clinical Practice Research Datalink (CPRD), which includes over 10 million primary care patients in the UK, shown to be representative of the population of the UK [3], and the Hospital Episodes Statistics (HES). This second database comprises records of all admissions conducted in NHS trust hospitals and independent treatment centres in England. The two databases were linked in order to identify all the incident cases either in primary or in secondary care, registered between April 1997 and August 2010. Date of death was available in the death registry data from the Office for National Statistics (ONS) or from CPRD records.

By linking the three databases Ratib and coworkers were able to assess 1- and 5-year average survival of patients with cirrhosis and the independent effect of hospitalization adjusted for age, sex, aetiology, and clinical stage of the disease. Overall, survival probabilities at 1- and 5-years were 0.70 (95% CI 0.69–0.71) and 0.47 (95% CI 0.45–0.48). Corresponding figures were 0.84 (95% CI 0.83–0.86) and 0.66 (95% CI 0.63–0.68) for the ambulatory group and 0.55 (95% CI 0.53–0.57) and 0.31 (95% CI 0.29–0.33) following hospitalization, respectively. A hospital admission for liver disease, substantially impaired prognosis, independent of stage of cirrhosis (HR = 2.78, 95% CI 2.53, 3.06). Stratified analyses by sex, time at risk, aetiology, and age showed that survival decreased with age, was better for women and was slightly different across different aetiologies.

A major strength of this large population based study is that it included patients with incident cirrhosis identified either in primary or in secondary care settings, thus assembling a cohort likely representative of the whole cirrhotic population, at least in UK. It provides unique and precise (narrow CI) information on overall survival of cirrhosis, on the incidence of hospitalization for ambulatory patients and on long term survival after hospitalization as well as on survival for patients remaining in an ambulatory setting. This information offers solid evidence for health care policy makers to plan appropriate resources for caring cirrhotic patients in UK.

However, applicability of the results in other areas should be carefully assessed, particularly with respect to the possible differences in aetiology and related differences in survival. As an example, a large population based study of survival of cirrhosis from Denmark showed very different prevalence of etiology of cirrhosis in a cohort of 10,154 hospitalized patients [4], and survival was markedly different according to aetiology, a finding different from the slightly different survival across different etiologies in the present study.

The key message of the study is that survival of cirrhosis is significantly higher in patients diagnosed and followed in an ambulatory setting than in patients with a first diagnosis in the occasion of a hospital admission. Therefore the Authors suggest that any effort should be done to prevent hospitalization to improve survival.

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Editorial

A major drawback of the study is, however, that the electronic databases used to assemble the included cohort did not contain any clinical information. Therefore the patient characterization is largely insufficient to translate the provided prognostic information into clinical practice. As an example, an average 1-year survival probability of 0.84 was estimated for the 2698 ambulatory patients. However we know from a number of previous studies that in mostly compensated patients, like the ambulatory patients in this study, a large proportion do have oesophageal varices [1] and a significantly lower survival than patients without varices. Moreover, although the ambulatory patients in this study were mostly compensated, 631 out of 2698 (23%) had a decompensated cirrhosis, 394 in stage 3 and 237 in stage 4 according to the Baveno IV classification [5]. The observed 1-year survival probability in these two disease stages (decompensated cirrhosis) is 0.80 and 0.43, respectively [1]. By contrast in stages 1 and 2 (compensated patients without or, respectively, with oesophageal varices) corresponding probabilities are 0.99 and 0.96 [1]. It is therefore hard to put the average survival probability reported by Ratib and coworkers in the clinical context without proper clinical characterization of patients from whom the estimates were derived and without appropriate subgroup analyses. Furthermore, several prognostic variables are also important for decision making. As an example, the knowledge of the presence of oesophageal varices informs personalized treatment decisions for the prevention of portal hypertensive bleeding that have a strong impact on patients outcome and hence on the disease burden for the health care system. Such kind of personalized decisions are based on the knowledge of the outcome of subgroups of patients with certain prognostic characteristics (varices, in this case) and of the efficacy of treatments (in this case beta-blockers or banding ligation of varices). The knowledge of only the average survival probabilities does not allow for any personalized clinical approach [6]. This consideration points out another weakness of the study: the lack of any information regarding the treatments given to the patients not only regarding the disease complications but also etiological treatments, like antiviral treatments for HBV or HCV infected patients.

Another major information provided by the Ratib *et al.* study is that 1021 of the 2698 (37.8%) ambulatory patients experienced an emergency hospital admission for liver related episodes. Unfortunately, no information was available regarding the type of the clinical events causing such hospital admissions. However, it is conceivable that hospital admissions were caused by acute decompensating events, like bleeding or encephalopathy, spontaneous bacterial peritonitis, acute on chronic liver failure, or others. Therefore, translating the information into actions from the health care system, may imply prompting adherence to recommendations for the prevention of decompensation in the primary care setting. As an example of the impact this may have, an Italian multicentre study of the outcome of variceal bleeding, in the early 2000s showed that a sizable proportion of patients admitted for bleeding had undergone neither beta-blockers nor band ligation, when these treatments were clearly recommended [7]: probably a higher adherence to recommendations for the prevention of variceal bleeding would have saved many of those bleeding episodes.

Finally, the Ratib's study, for the first time, reports post-hospitalization survival of cirrhotic patients and shows that hospitalization marks a turn point in the clinical course of cirrhosis. After hospitalization 1- and 5-year survival probabilities were 0.55 and 0.31, respectively, a figure markedly lower than that usually reported after the first decompensating event. This is likely due to the fact that hospitalization was associated with some emergency condition, thus selecting patients with more severe disease. Again, the lack of any characterization of hospitalized patients and of any prognostic subgroups analysis, makes this information of use only for health care policy makers, while it may not help personalized decision making.

In summary, the study by Ratib and colleagues provides important average and precise estimates of survival of cirrhosis from a large population based study, likely representative of the cirrhotic population in UK. It also raises, some important considerations. First, large well settled health system administrative databases may offer the unique opportunity to draw important information like that provided in the present study; second, this kind of information may be of use for health care policy makers who have to plan population oriented health care resources; third, this kind of information is not any more of use in clinical practice where an individualized approach to the care of patients is more and more needed to optimize the efficiency of care.

Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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