



Liver transplantation for non-alcoholic steatohepatitis in Europe: Where do we stand?

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Red flags have recently been raised concerning the growing burden of non-alcoholic steatohepatitis (NASH) in liver transplantation. Interestingly most large studies on NASH in liver transplantation have come from the US for at least two reasons. Firstly, there has been a more rapid increase in the prevalence of obesity and type-2 diabetes mellitus, two major risk factors for non-alcoholic liver disease (NAFLD) and NASH, in the US than in European and Asian countries.¹ The burden of NAFLD/NASH is currently higher in the US than in Europe, as the US has the highest number of obese adults in the world. With the success of direct-acting antivirals, the number of transplantations for hepatitis C virus (HCV) infection has drastically decreased and NASH is now the second most common indication for liver transplantation in the US.² Among those on the liver transplant waitlist due to hepatocellular carcinoma (HCC), NASH-related HCC prevalence increased 11.8-fold from 2002 to 2016, the fastest growing cause of HCC. Second, US nationwide data concerning liver transplantation have been prospectively implemented by all transplant centres in the administrative Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) registry since 1988. The OPTN/UNOS dataset allowed for robust epidemiological studies, even if exhaustivity and accuracy of data have been a matter of concern. Standardised collection of data helped analyse trends in liver transplantation in the US. We have learned from the US registry that patients transplanted for NASH are older than patients transplanted for other indications.³ Patients waitlisted for NASH have more comorbidities including impaired kidney function.⁴ NASH is the most rapidly growing indication for simultaneous liver and kidney transplantation.⁵ Post-transplant mortality due to cardiovascular diseases is higher in patients with NASH than other aetiologies.⁶ Analysis of the OPTN/UNOS registry suggests that post-transplant survival in patients with NASH is not inferior to that in patients transplanted for other

chronic liver diseases.^{3,7} However, findings in the US may not be directly applicable to Europe. Until now, European data concerning NASH and transplantation have been scarce since no large administrative registry covering all European countries has been published.

In this issue, Haldar and colleagues report the results of a large European registry, European Liver Transplant Registry (ELTR) aimed at analysing trends in liver transplantation for NASH throughout 174 transplant centres in 33 European countries.⁸ In this study 2,741 patients with NASH (43% with NASH and 57% with presumed NASH) transplanted between 2002 and 2016 were included. The proportion of patients transplanted for NASH increased from 1.2% in 2002 to 8.4% in 2016. Among patients transplanted for NASH, 39.1% had HCC. Post-transplant survival was not significantly different in patients with and without NASH after adjusting for confounding factors. In patients with NASH and no HCC, advanced age, high model for end-stage liver disease score (>23) and low (<18 kg/m²) or high (>40 kg/m²) body mass index (BMI) were predictive of post-transplant mortality. Overall, this registry study confirms that NASH is also a growing indication for liver transplantation in Europe. This study also represents a global perspective that enables comparison of liver transplantation for NASH in Europe and the US.

There are many similarities between Europe and the US. In both Europe and the US, the proportion of patients transplanted for NASH increased during the last decade. Again, this trend resulted from an increasing burden of diabetes and obesity, and control of HCV epidemics.⁹ In both Europe and the US, the proportion of patients transplanted for HCC among those with NASH increased over time.^{3,8} Patients with NASH are older at transplantation. In general, post-transplant outcomes are similar in NASH and non-NASH patients, with or without HCC, despite the theoretic concern of negative impact of comorbid conditions in patients with NASH. In Europe as well as in the US, cardiovascular complications and sepsis were the major causes of death in patients transplanted for NASH. Recurrence of NASH seems to be a marginal cause of death or graft loss.⁸

There are also important differences between Europe and the US. In the report from the HEPAHEALTH project, which investigated the burden of liver diseases in 35 European countries, NAFLD/NASH still represents a relatively small cause of

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cirrhosis, which translates into a relatively small proportion of candidates for transplantation.¹⁰ In the European study by Halder *et al.*,⁸ NASH only accounted for 4% of the transplantations (reaching 8.4% in 2016) after excluding retransplantation, multiple organ transplantation and emergency transplantation. Using similar exclusion criteria, the proportion of patients transplanted for NASH was 19% in a recent study in the US.⁶ Even though the ELTR registry does not allow comparison between different countries, there are significant geographic variations within Europe, more so than in the US. There are some countries that bucked that overall trend, with stable and even declining rates. In European countries with rising obesity rates, there was already an increase in NAFLD-related mortality with a time lapse. The proportion of patients with NASH who died from cardiovascular or cerebrovascular complications was twofold higher in the US (11.5%) (6) than in Europe (5.3%),⁸ which may reflect different profiles or differences in coding.

The ELTR study highlights important aspects of NASH and transplantation in Europe. It also has several limitations of a registry study, some of which are common to studies based on the US OPTN/UNOS registry. NASH was only added to the ELTR database as a separate category in 2012, and from 2012 to 2017, NASH accounted for only 2.7% of liver transplant recipients. More than 50% of patients were not coded as NASH but were considered to have presumed NASH. The authors have to be congratulated on their use of the same definition of presumed NASH as in US studies (cryptogenic cirrhosis or cirrhosis of unknown origin and BMI ≥ 30 kg/m²) which facilitates comparisons.² However, a significant proportion of patients may be misclassified *e.g.* due to water retention. Similarly, cases of burnt-out NASH in patients with poor nutritional status and BMI < 30 kg/m² may be considered as cryptogenic cirrhosis. The ELTR also lacks key variables such as diabetes mellitus and pre-transplant cardiovascular diseases. Patients with simultaneous liver and kidney transplantation were excluded leading to an underestimate of the burden of chronic kidney disease. Data on waiting list mortality were not available. Geographic variations between different European countries could not be analysed. Finally, the number of missing key data was very important. In multivariate analysis, cases with missing data had to be assigned to a separate missing category which is a source of bias.

The results of this study must be interpreted with caution due to the inherent limitations of the ELTR registry. Similar limitations exist with the UNOS/OPTN registry. However, these large registries have to be used to better anticipate changes in disease profiles. Recent official documents produced by the Food and Drug Administration,¹¹ European Medicines Agency members¹² and important international pharmacoepidemiology and drug-safety associations¹³ refer to real-world evidence (RWE) studies as a need and a challenge at the same time for medical research. RWE includes data from observational studies, registries and electronic records, which public health agencies are recognising as extremely relevant to generate new hypotheses and estimate the burden of a specific disease while accounting for geographical variability. Agencies need RWE to support their decisions, while investigators need to run these studies to integrate the information generated in clinical trials and assess its validity in the real world. To be useful, real-world data must be relevant, reliable and quality-controlled. RWE quality involves specific strategies for minimising missing or

incomplete data. Good procedural practices for these studies must include transparency and reproducibility of all study steps. RWE fulfilling these criteria provides insights beyond those addressed by clinical trials and can be crucial to improve medical knowledge and health care decision-making.

Hepatologists and the liver transplant community will all have to face the burden of NASH. Liver transplant registries have clearly shown that NASH weighs heavily on the waiting list and that the profile of liver transplant recipients is changing in the US. The ELTR study suggests that until now, NASH has had a more limited impact on liver transplantation in Europe. Large registries, whether administrative or not, are useful tools to analyse the present situation and to anticipate the future. It is encouraging that the reported liver transplant outcomes are similar in patients with NASH and those transplanted for other aetiologies. However, it is hardly conceivable that transplanting older patients with more comorbidities results in similar outcomes in the long term. Therefore, more granular data collection is now needed to really understand why and how NASH matters in liver transplantation.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2019.05.018>.

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