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NAFLD/NASH

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Nonalcoholic fatty liver disease is an increasing indication for liver transplantation in the Nordic countries

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Abstract

Background & Aims: Nonalcoholic fatty liver disease(NAFLD) is the second most common cause of liver transplantation in the US. Data on NAFLD as a liver transplantation indication from countries with lower prevalences of obesity are lacking. We studied the temporal trends of NAFLD as an indication for liver transplantation in the Nordic countries, and compared outcomes for patients with NAFLD to patients with other indications for liver transplantation.

Method: Population-based cohort study using data from the Nordic Liver Transplant Registry on adults listed for liver transplantation between 1994 and 2015. NAFLD as the underlying indication for liver transplantation was defined as a listing diagnosis of NAFLD/nonalcoholic steatohepatitis, or cryptogenic cirrhosis with a body mass index ≥25 kg/m^2 and absence of other liver diseases. Waiting time for liver transplantation, mortality and withdrawal from the transplant waiting list were registered. Survival after liver transplantation was calculated using multivariable Cox regression, adjusted for age, sex, body mass index and model for end-stage liver disease.

Abbreviations: ALD, alcoholic liver disease; BMI, body mass index; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; INR, international normalized ratio; LTX, liver transplantation; MELD, model for end-stage liver disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NLTR, the Nordic liver transplant registry.

Results: A total of 4609 patients listed for liver transplantation were included. NAFLD as the underlying indication for liver transplantation increased from 2.0% in 1994-1995 to 6.2% in 2011-2015 (P = .01) and was the second most rapidly increasing indication. NAFLD patients had higher age, model for end-stage liver disease and body mass index when listed for liver transplantation, but overall survival after liver transplantation was comparable to non--NAFLD patients (aHR 1.03, 95% CI 0.70-1.53 P = .87).

Conclusion: NAFLD is an increasing indication for liver transplantation in the Nordic countries. Despite more advanced liver disease, NAFLD patients have a comparable survival to other patients listed for liver transplantation.

KEYWORDS

Liver cirrhosis, NASH, NLTR, obesity

1 | INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has become the most common liver disease globally.[1,2] NAFLD is closely associated with obesity, diabetes type 2 and the metabolic syndrome.[3] Previously, NAFLD has been underdiagnosed, and it is now approximated that 50% of patients previously diagnosed as cryptogenic cirrhosis did in fact have NAFLD.[4,5] Most NAFLD patients do not develop end-stage liver disease, but approximately 20% will develop nonalcoholic steatohepatitis (NASH), of which 20%-40% will develop progressive liver fibrosis and of these, 10%-20% progress further to cirrhosis.[6,7] Patients suffering from cirrhosis can deteriorate and develop decompensated cirrhosis, and are at an increased risk of developing hepatocellular carcinoma (HCC).[8] Altogether the liver-specific mortality for NAFLD patients is approximately 6%.[5,9-11] For patients suffering from decompensated cirrhosis or HCC, liver transplantation (LTX) is the most beneficial and often the only curative treatment option.[12,13]

Recent studies from the US show that NASH as an indication for LTX has increased by 170% between 2004 and 2013, making NASH the second most common cause after hepatitis C cirrhosis for need of LTX among adults in the US.[14] Taking into account the effects of new effective treatments for chronic hepatitis C infection (HCV), a decrease in the number of HCV patients listed for LTX is projected.[15] The US data on NAFLD and LTX suggest that NASH will surpass HCV as the number one indication for LTX in the US in the near future.

Reports from the Centers for Disease Control and Prevention show that the prevalence of obesity (defined as a body mass index [BMI] ≥30 kg/m^2) in the US has increased from 30.5% to 37.7% from 1999 to 2014.[16] Data on NAFLD as an indication for LTX from countries with lower prevalences of obesity are lacking. Although obesity has increased notably in the Nordic countries, the prevalence is low compared to the US, ranging between 13.4% and 19.0%.[17-20] The spectrum of other liver diseases in the Nordic countries is also different compared to the US. Autoimmune liver diseases have been the most common indications for LTX since it was introduced as a treatment modality in the Nordic countries in the early 1980s.[21]

Key points

- In the Nordic countries, nonalcoholic fatty liver disease (NAFLD) was the second most rapidly increasing indication for liver transplantation between 1994 and 2015.
- During the study period, the relative increase of NAFLD as an indication for liver transplantation was 153%.
- This trend was paralleled by an increased prevalence of obesity in the Nordic countries and in patients listed for liver transplantation.
- Mortality for NAFLD patients after liver transplantation was comparable to that of non-NAFLD patients.

In addition to liver disease, NAFLD patients commonly have other comorbidities related to obesity such as diabetes type 2, hypertension and cardiovascular disease.[5,10] This puts NAFLD patients at a higher risk for complications following LTX.[22,23] BMI has been shown to be an independent risk factor for post-operative mortality after LTX and previous studies have demonstrated that even though NAFLD patients have a comparable survival following LTX, they have a higher risk of cardiovascular complications and sepsis-related mortality.[24] Also, NAFLD patients have an increased risk of recurring NAFLD and graft fibrosis post-LTX.[25,26]

1.1 | Aim

The aim of this study was to investigate if NAFLD is increasing as an indication for LTX in the Nordic countries compared to other liver diseases. We also aimed to determine if NAFLD patients have higher mortality after LTX compared to other indications.

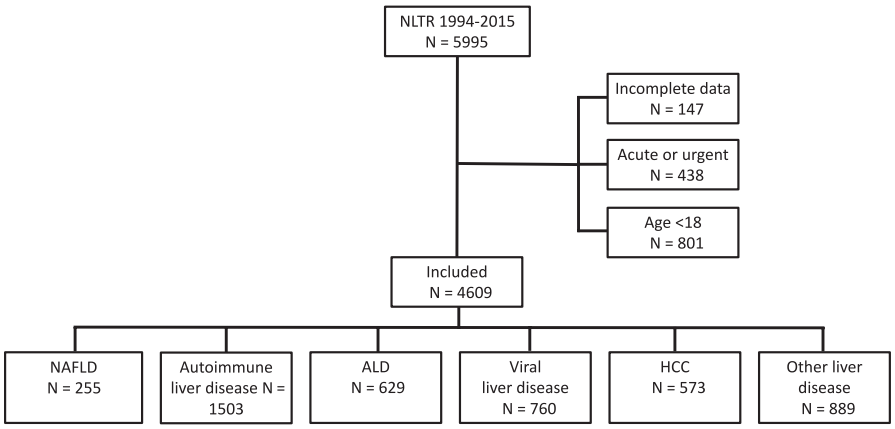

FIGURE 1 Flow chart of study design and patient inclusion. Abbreviation: ALD, Alcoholic liver disease; HCC, Hepatocellular carcinoma; NAFLD, nonalcoholic liver disease; NLTR, Nordic Liver Transplant Registry

2 | MATERIALS AND METHODS

2.1 | Study population and data collection

We used data from the Nordic Liver Transplant Registry (NLTR). The NLTR contains data from all transplantation centres in Denmark, Sweden, Norway and Finland since 1982, with data on BMI available since 1994. Cases listed for LTX between 1982 and 1993 were therefore excluded (N = 825). Between 1994 and 2015, 5995 patients were listed for LTX. From this cohort we excluded patients younger than 18 years (N = 801), cases where the indication for LTX was defined as highly urgent (these most likely did not represent typical NAFLD) (N = 438) and cases where data on height or weight were missing (N = 147). In total, 4 609 patients were included in the study (Figure 1).

Diagnoses in NLTR are coded by a specific classification system comprised by more than 90 different diagnostic codes. Data on serologic markers for hepatitis B and C (HBV/HCV) are also available. We defined 6 specific groups based on these data. The congregated groups of diseases included: (i) NAFLD, (ii) autoimmune liver disease, (iii) alcoholic liver disease (ALD), (iv) chronic viral hepatitis, (v) HCC and (vi) other liver diseases. For a detailed description of these groups, see the Table S1.

We used 2 different approaches to define patients as NAFLD cases. Firstly, patients with specific coding for NAFLD/NASH were defined as NAFLD cases. Secondly, patients who were registered as cirrhosis of unknown cause or as cryptogenic cirrhosis, with a BMI ≥25 kg/m^2 at the time of listing for LTX and with no coding for any other liver disease were also defined as NAFLD cases. This method for defining NAFLD retrospectively is similar to that used by other authors.[14,27,28] Except for data on height and weight, no data on the presence of type 2 diabetes or other traits of the metabolic syndrome was available in the NLTR.

The definition of chronic viral hepatitis was based on either a specific code or positive serologic markers for HBV or HCV. In the classification, HBV or HCV positivity was overriding the coexistence of alcoholic liver disease and autoimmune liver disease. For patients registered as HCC, there was limited data in the NLTR accounting for any underlying liver disease. Patients that did not fit into any of the categories described above were classified as other liver disease (Table S1).

To analyse temporal trends, the study population was stratified into 5 time periods based on the year of listing for LTX: 1994-1995, 1996-2000, 2001-2005, 2006-2010 and 2011-2015. Temporal trends for BMI for all cases included in the study were calculated. Additionally, temporal trends for BMI for cases classified as HCC were calculated separately.

Data on bilirubin, INR and creatinine levels at time of listing were used to calculate Model for End-Stage Liver Disease scores (MELD).[29] The NLTR also contains data on history of ascites, defined as if the patient had ascites at any time before listing for LTX.

2.2 | Ethical considerations

The study was approved by the Regional ethical committee at Karolinska Institutet, Stockholm, Sweden. Dnr 2015/1011-31/2.

2.3 | Statistical analysis

Continuous data is presented as medians and categorical data as percentages. Differences between patients with NAFLD and other indications for LTX were calculated using the Chi^2 test for categorical parameters, and the Mann-Whitney U-test for continuous parameters. Changes in median BMI during the study periods were calculated using the Kruskal-Wallis test. Temporal trends were estimated as the percentage of the number of LTXs during each of the 5 time periods for each of the 6 diagnostic groups, using a non-parametric test for trend.[30] The relative increase for each diagnostic group was calculated as the increase in per cent of the absolute number of cases from the second time period (1996-2000) to the last time period (2011-2015). The first time period (1994-1995) was excluded from this calculation because of a small number of cases (N = 198).

Mortality after LTX was estimated comparing NAFLD patients to all non-NAFLD patients using multivariable Cox regression in 2 separate models. In the first model, we adjusted for sex, age at listing for LTX and BMI. In the second model, we further adjusted for MELD score. The Kaplan-Meier method was used to calculate survival curves.

TABLE 1 Characteristics of study population

	Complete data (n)	NAFLD (n = 255)	Non-NAFLD (n = 4354)	*P*-value
Age, y, median (IQR)	4609	57.9 (50.7-63.0)	52.8 (43.4-59.6)	<.001
Male, n (%)	4609	161 (63.1)	2,664 (61.2)	.53
BMI kg/m^2, median (IQR)	4609	28.4 (26.7-31.2)	24.3 (21.9-27.5)	<.001
Creatinine, µmol/L, median (IQR)	3706	83 (68-113)	73 (60-92)	<.001
INR, median (IQR)	2540	1.5 (1.3-1.9)	1.3 (1.1-1.6)	<.001
Bilirubin, µmol/L, median (IQR)	3701	46 (25-97)	41 (19-97)	.14
MELD, median (IQR)	2533	16.8 (12.6-21.5)	13.5 (9.4-18.1)	<.001

BMI, Body Mass Index; INR, International Normalized Ratio; MELD, Model for End-stage Liver Disease.

Characteristics of patients listed for liver transplantation in the Nordic countries 1994-2015. Paediatric patients, highly urgent cases and cases with incomplete data on BMI excluded.

In sensitivity analyses, we first defined NAFLD as in the main analysis but using a BMI cut-off of 30 kg/m^2. Secondly, because of risk of recurrence of HCC or viral hepatitis after LTX, which could have negative effect on long-term survival, we estimated survival in NAFLD compared to other liver diseases but excluding cases with HCC or viral hepatitis. All analyses were performed in STATA v 13.0 (STATACORP, College Station, Tx, USA).

3 | RESULTS

3.1 | Cohort characteristics

Of the included 4609 patients, 255 were identified as NAFLD cases. Demographical and clinical characteristics of patients at the time for listing for LTX are presented in Table 1. Forty-four NAFLD patients were identified by specific coding for NAFLD/NASH and 211 patients met the criteria of having cryptogenic cirrhosis in combination with a BMI ≥25 kg/m^2 and no other liver disease. Patients with NAFLD were older compared to other patients (57.9 vs 52.8 years, *P* < .001), had higher BMI (28.4 vs 24.3 kg/m^2, *P* < .001) and higher MELD scores (16.8 vs 13.5, *P* < .001) at the time of listing for LTX. Complete data for calculating MELD was available for 2533 patients (55%). The gender distribution among NAFLD patients was comparable to non-NAFLD patients (63.1% vs 61.2% men, *P* = .53). Of the total study population, 52.2% had a history of ascites at the time of listing for LTX. The proportion of NAFLD patients with a history of ascites was significantly lower compared to patients with ALD and viral liver disease grouped together (70.1% vs 77.5%, *P* = .03).

The median BMI of the study population increased significantly during the study period from 22.9 kg/m^2 in the first period to 25.2 kg/m^2 in the last period (*P* < .001). The prevalence of overweight (BMI 25-30 kg/m^2) and obesity (BMI ≥30 kg/m^2) increased from 20.2% and 4.0%, respectively in the first period to 35.0% and 17.2% in the last period (both *P* < .001) (Figure 2). The median BMI for HCC patients increased from 22.6 kg/m^2 in the first period to 27.5 kg/m^2 in the last period (*P* < .001).

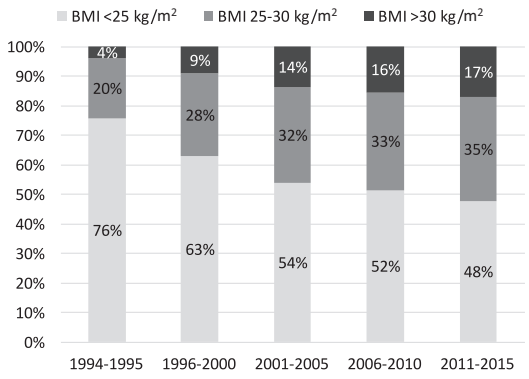

FIGURE 2 Temporal trend on distribution between normal weight (BMI <25 kg/m^2), over weight (BMI 25-30 kg/m^2) and obesity (BMI ≥30 kg/m^2) in the total study population between 1994 and 1995 and 2011 and2015. Abbreviations: BMI, body mass index

3.2 | Indications for liver transplantation

Of the total population, the proportion of patients who were listed for LTX owing to NAFLD increase from 2.0% in the first period (1994-1995) to 6.2% in the last period (2011-2015) (*P* .01). HCC was the diagnosis with the highest relative increase, from 3.5% of all cases in the first period to 19.7% in the last period (*P* < .001). Data

TABLE 2 (a) Temporal trends in BMI at listing on waiting list for LTX. Changes in median BMI calculated using the Kruskal-Wallis test. *P*-value for significance of temporal trends between 1994 and 1995 to 2011 and 2015. (b) Temporal trends in indications for LTX in the Nordic countries between 1994 and 2015. Data is presented as absolute numbers of patients and percentages per each time period. Data on the changes in each indication for LTX was analysed using a test for trend. *P*-value for significance of temporal trends between 1994 and 1995 to 2011 and 2015

	Transplantation period					
(a)	1994-1995	1996-2000	2001-2005	2006-2010	2011-2015	*P*
BMI category						
BMI <25 kg/m^2, %	75.8	62.9	53.9	51.5	47.8	
BMI 25-30 kg/m^2, %	20.2	27.9	32.3	33	35	
BMI >30 kg/m^2, %	4.0	9.2	13.8	15.5	17.2	
BMI, median (IQR)	22.9 (21.0-24.9)	23.9 (21.4-26.7)	24.6 (22.0-27.7)	24.8 (22.1-28.1)	25.2 (22.5-28.4)	<.001
(b)	1994-1995 n (%)	1996-2000 n (%)	2001-2005 n (%)	2006-2010 n (%)	2011-2015 n (%)	*P*
Autoimmune liver disease	81 (40.9)	254 (34.0)	306 (33.4)	407 (32.0)	455 (30.8)	.007
Alcoholic liver disease	27 (13.6)	100 (13.4)	143 (15.6)	158 (12.4)	201 (13.6)	.57
Chronic viral hepatitis	26 (13.1)	136 (18.2)	164 (17.9)	226 (17.8)	208 (14.1)	.002
Other liver disease	55 (27.7)	173 (23.2)	180 (19.7)	251 (19.7)	230 (15.6)	<.001
NAFLD	4 (2.0)	36 (4.8)	48 (5.2)	76 (6.0)	91 (6.1)	.01
HCC	5 (2.5)	47 (6.3)	75 (8.2)	155 (12.2)	291 (19.7)	<.001
Total	198	746	916	1273	1476	

BMI, Body Mass Index; HCC, Hepatocellular Carcinoma; LTX, liver transplantation.

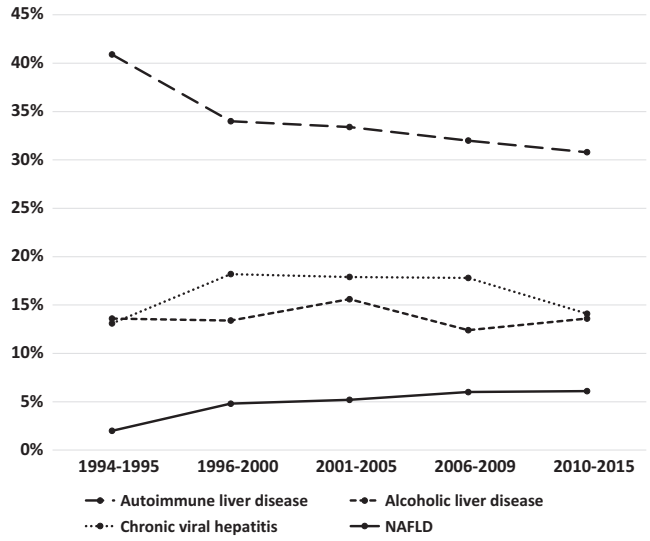

FIGURE 3 Frequency of nonalcoholic fatty liver disease (NAFLD), autoimmune liver disease, chronic viral hepatitis and alcoholic liver disease as indications for liver transplantation (LTX), shown as % of total number of LTX for each time period

on temporal trends in LTX indications and BMI are presented in Table 2. Temporal trends for NAFLD compared to other chronic liver diseases (HCV, ALD and autoimmune liver disease) are presented graphically in Figure 3.

During the study period, all transplant indications increased in absolute numbers. Between 1996 and 2000, 36 patients were transplanted because of NAFLD. This number increased to 91 patients between 2011 and 2015, with an increase of 153%. NAFLD showed the second highest relative increment rate after HCC, that increased by 519% between the second and the last time period, from 47 to 291 cases. The relative increase for other groups of diagnoses were: 33% for other liver diseases, 53% for chronic viral hepatitis, 79% for autoimmune liver disease and 101% for ALD.

3.3 | Outcomes after listing for liver transplantation

There were no significant differences in waiting time or mortality while on the waiting list for LTX, or any increased risk of withdrawal from waiting list for NAFLD patients compared to patients being listed for LTX for other causes (Table 3).

3.4 | Outcomes after liver transplantation

Mortality after LTX for NAFLD patients was comparable to that of non-NAFLD patients, with a similar post-operative 90-day mortality in both unadjusted analysis (HR 1.36 95% CI 0.71-2.59, *P* = .35) and when adjusted for age, sex, BMI and MELD (aHR 2.20 95% CI 0.88-5.51, *P* = .09). After both 1 year (aHR 1.39 95% CI 0.73-2.62,

TABLE 3 Risk estimates during time on waiting list

	Autoimmune liver disease	Alcoholic liver disease	Chronic viral hepatitis	Other liver disease	NAFLD	HCC	All non-NAFLD	*P*-value*
Death on waiting list, %	3.1	7.3	5.0	3.2	3.1	1.4	4.0	.47
Withdrawal from waiting list, %	6.4	6.5	6.4	9.9	6.3	10.2	7.4	.51
Waiting time, days, median (IQR)	47 (17-117)	31 (12-74)	45 (17-100)	40 (13-113)	38 (13-96)	29 (13-61)	41 (15-99)	.56

Risk of death during time on waiting list, withdrawal from waiting list and waiting time. No significant differences were observed between the 6 diagnoses groups.

*P-value for nonalcoholic fatty liver disease (NAFLD) compared to all non-NAFLD.

TABLE 4 Mortality after liver transplantation

	Model 1			Model 2			Model 3		
	HR	95% CI	*P*	aHR	95% CI	*P*	aHR	95% CI	*P*
90 days	1.36	0.71-2.59	.35	1.15	0.59-2.25	.67	2.20	0.88-5.51	.09
1 year	1.38	0.93-2.06	.11	1.8	0.84-1.93	.25	1.39	0.73-2.62	.31
5 years	0.92	0.66-1.27	.60	0.82	0.59-1.15	.25	0.80	0.48-1.31	.37
Total	1.06	0.83-1.36	.65	0.92	0.72-1.19	.53	1.03	0.70-1.53	.87

BMI, body mass index; CI, confidence interval; HR, hazard ratio.

Hazard ratios for overall mortality after liver transplantation for nonalcoholic fatty liver disease (NAFLD) patients compared to all other indications for liver transplantation. Model 1, unadjusted estimates. Model 2, adjusted for age, sex and BMI. Model 3, further adjusted for MELD.

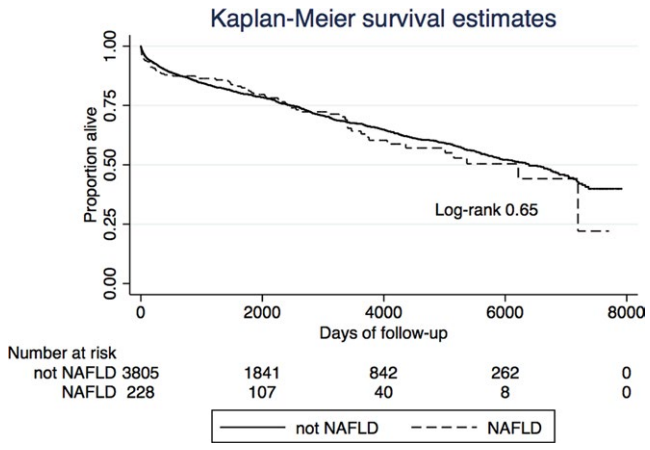

FIGURE 4 Kaplan-Meier estimate showing post-transplant survival for nonalcoholic fatty liver disease (NAFLD) patients compared to all other liver disease (Non- NAFLD) during total time of follow-up

P = .31) and 5 years (aHR 0.80 95% CI 0.48-1.31, *P* = .37) of follow-up, no difference in mortality was observed. Data on mortality are presented in Table 4. Finally, overall mortality after a total of 26 187 person-years, showed no difference between NAFLD and non-NAFLD patients (aHR 1.03 95% CI 0.70-1.53, *P* = .87) (Figure 4). Re-transplantation was performed in 3% of NAFLD patients vs 8% in other indications (*P* = .006). Mean graft survival time was 6 years in NAFLD vs 6 years in other indications (*P* = .63).

3.5 | Sensitivity analysis

Changing the cut-off for BMI from ≥25 kg/m^2 to ≥30 kg/m^2 in the definition of NAFLD yielded fewer cases (N = 91 vs 255). Using this definition, NAFLD as a transplant indication increased from 0.50% of total cases in the first period to 2.7% in the last period (*P* < .001). Mortality after LTX or during the waiting time was similar as in the main analysis, as were duration of waiting time and proportion of withdrawal from the waiting list (data not shown).

When comparing NAFLD to other liver diseases but excluding cases with HCC and viral hepatitis, no significant change in mortality estimates was found (adjusted HR for overall survival 1.03, 95% CI 0.70-1.53, *P* = .87).

4 | DISCUSSION

The results from this multinational, population-based cohort study from 1994 to 2015 show that NAFLD was the second most rapidly

increasing indication for LTX in the Nordic countries. This indicates that end-stage liver disease caused by NAFLD is a growing problem also in countries with lower prevalence rates of obesity than in the US. However, this increase has occurred from a small number of patients, and NAFLD still accounts for a small proportion of patients being listed for LTX in the Nordic countries.

The epidemic increase of obesity and type 2 diabetes has led to NAFLD being the most common chronic liver disease globally. In the study based on data from United Network for Organ Sharing and Organ Procurement and Transplantation Network registry, Wong et al[14] demonstrated that NAFLD as a cause for liver transplantation increased in the US by 170% from 2003 to 2013. NAFLD was the diagnosis that increased most rapidly, compared to ALD, HCV and combined ALD/HCV. Other studies from the US have also demonstrated a rapid increase of NAFLD patients being listed for LTX in relation to patients with other liver diseases.[27,31,32] Obesity in the Nordic countries has increased during the last decades, which we here show is valid also for patients listed for LTX, but the prevalence of overweight and obesity reported from this region of the world is still substantially lower compared to the US.[16-20] Nevertheless, the major results from our study are consistent with the results from American studies. European data on the epidemiology of NAFLD as an indication for LTX is lacking. From the European network of liver transplantation, Eurotransplant, one report describes the distribution between groups of diagnoses listed for transplantation, but this report does not study the temporal trends and does not identify NAFLD as a diagnostic group of its own.[33] Therefore, our study brings important new knowledge to this field from a European perspective.

During the study period, the diagnosis with the highest relative increase was HCC. This was previously shown in a separate study from the NLTR, that also included cases with missing data on BMI.[13,21] Before the establishment of generally accepted criteria for LTX as a treatment, HCC as an indication for LTX was a subject of debate. It is therefore difficult to interpret the rapid increase of HCC patients in our study when this could be attributed to better identification and selection of HCC cases suitable for LTX.[34]

Nonalcoholic fatty liver disease patients are at increased risk of surgical complications and post-surgical mortality following LTX owing to obesity-related risk factors.[24,27,35] Patients with more comorbid diseases are also at a higher risk of deteriorating while on the waiting list and consequently, of being withdrawn from the waiting list. However, we found no increased risk for waiting-time mortality in NAFLD patients. This might be partly explained by the relatively high organ availability in the Nordic countries. Indeed, only 4 per cent of listed patients died while on the waiting list in this study. Moreover, we found no differences in either short- or long-term survival after LTX for NAFLD patients compared to patients with other liver diseases, although we did observe a trend for a higher 90-day mortality for NAFLD patients when adjusting for age, sex, BMI and MELD. Based on these results, we argue that the long-term benefit for NAFLD patients who are listed for LTX in the Nordic countries is similar to that of patients with other liver diseases. Data on the trend in mortality rates according to each time period has previously been described elsewhere.[13]

The major limitation of our study is the risk of misclassification bias when defining cases as NAFLD based on retrospective register data. NAFLD was previously a rather unknown disease and has been underdiagnosed.[36] Our methodology, that included all patients with cirrhosis of unknown cause and BMI ≥25 kg/m^2, can be criticized for being less precise than models used in previous studies that mostly have used a higher cut-off for BMI at ≥30 kg/m^2. However, when defining NAFLD using 30 kg/m^2 as a cut-off, we found fewer NAFLD-cases but similar results in temporal trends as when using the BMI cut-off of 25 kg/m^2. We know today that NAFLD can occur in patients who are modestly overweight, or even have a normal BMI, especially in combination with other traits of the metabolic syndrome or with genetic predisposition.[37] Therefore we believe the definition of NAFLD used in our study is correct.

Another concern about the identification of NAFLD patients using BMI is the influence on bodyweight from ascites. BMI was calculated using data on weight at the time of listing for LTX. We found that more than half of LTX-patients had ascites at some point during the course of their disease. The NLTR do not specify whether ascites was present at the specific time of listing, and therefore would also have impact on the accounted bodyweight, or only present at any time previous to listing. Presence of ascites was significantly less common in NAFLD compared to the other 2 groups that mainly includes patients with decompensated cirrhosis, ALD and chronic viral hepatitis. This suggests that, even though some individual patients could be misclassified as NAFLD owing to ascites causing a misleadingly high BMI, this is not a misclassification that affects the whole NAFLD group as defined in our study. On the other hand, some NAFLD cases might have lost bodyweight because of sarcopenia caused by end-stage liver disease[38] and could be misclassified as non-NAFLD. Unfortunately, no data on malnutrition or sarcopenia was available. The increase in BMI among LTX patients shown in our study is paralleled by a general increase of obesity reported from the Nordic countries. However, we cannot reject the possibility that the increase of BMI of LTX-patients over the study period is in part an effect of changed surgical policies allowing for more obese patients to be evaluated for LTX. Unfortunately, our data does not contain information from the 7 different LTX centres on changed guidelines or policies.

Also, we lack detailed information about important comorbid diseases, such as diabetes type 2 and other traits of the metabolic syndrome. With this information, the classification of NAFLD patients could have been more accurate. The limited data regarding primary liver diseases in the HCC group did not allow us to further sub-classify HCC cases. Nevertheless, we could show an increase of overweight and obesity in the HCC group, as expressed by increase in BMI. This makes it plausible that in part, the large increase in the number HCC patients in our study can be attributed to cases with NAFLD as the underlying liver disease.

5 | CONCLUSION

In this population-based cohort study, NAFLD as an indication for liver transplantation increased significantly in the Nordic countries between 1994 and 2015. Still, NAFLD accounts for a relatively small proportion of LTX indications. Mortality in NAFLD was comparable to other liver diseases listed for LTX. Taking into account the slow progress of NAFLD to cirrhosis and the increasing prevalence of obesity in the Nordic countries, our findings raise concerns on the future societal burden of NAFLD also on the outside of the US.

CONFLICT OF INTEREST

The authors do not have any disclosures to report

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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