The Nordic Liver Transplant Registry (NLTR)

Annual report 2018

Report prepared by Espen Melum June 2019

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1. Source of data

The numbers and graphs included in the present report are based on data extracted from the Nordic Liver Transplant Registry (NLTR) in April 2019. Prior to the export, data were subjected to extensive integrity and quality control. Entry of missing data and correction of all identified errors were performed at all centers prior to the final data extraction.

2. Data content NLTR 2018

The registry comprises complete data from the liver transplantation activity at all transplantation centers in Denmark, Sweden, Norway and Finland since 1982. Before 1990, only patients that were transplanted were registered. After 1990, the registry covers all patients entered to the liver transplantation waiting list, regardless of transplantation status. From September 1994, complete waiting list data are available from all patients in addition to the transplantation details. From October 1st 2017 data on patients transplanted in Estonia are prospectively included, patients transplanted in Estonia prior to this date have been retrospectively included. All data are stored securely at Scandiatransplant in Århus (www.scandiatransplant.org).

Up to December 31st 2018, data from a total of 8069 patients had been entered into NLTR. Of these, 7063 patients had received a first liver graft, 714 (10.1%) had been transplanted more than once, and 102 (1.4%) had been transplanted more than twice. Of the 714 patients receiving a second liver graft 7 had received their first graft outside of the Scandiatransplant area. A total of 176 living donor transplantations had been performed. Children below 18 years constituted 773 (10.9%) of the transplanted patients in the registry.

3. Transplantation activity 2018

The total number of patients who received a first liver graft in 2018 was 351 (Figure 1). Of these, 7 were combined liver-kidney transplantations and 2 were multivisceral. Of the first liver transplantations performed in 2018 2 were living donor transplantations while no domino transplantations were performed. The two living donor transplantations were performed in Stockholm and Oslo. Both multivisceral transplantations were performed in Gothenburg. In addition, 26 re-transplantations were performed (Table 2). The total number of liver transplantation was 377, this is a marked decrease compared with the 409 in 2017. This number now includes Estonia. If the Estonian patients are excluded the number is 367 which is a decrease of 9% compared to 2017 and 12% compared with 2016. The reduction in the number of retransplantations is even more marked with a decrease of 41% compared to 2017 and 50% compared with 2016 (Figure 1).

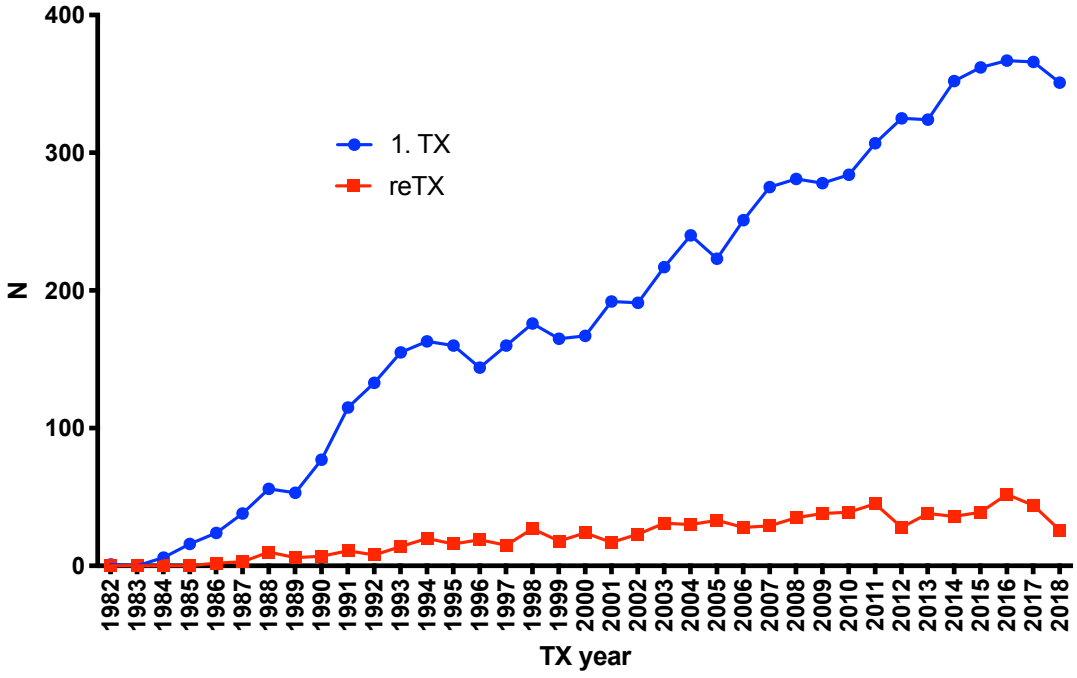

Figure 1. Number of patients receiving a liver allograft 1982-2018. The blue line represents the number of patients receiving a first liver graft while the red line represents the total number of re-transplantations.

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Copenhagen	35	43	43	43	39	41	55	51	52	39
Gothenburg	78	61	66	76	72	89	86	88	84	83
Helsinki	42	47	52	48	44	56	70	54	57	60
Oslo	69	77	81	89	96	89	72	88	85	87
Stockholm	43	53	65	68	73	77	79	86	82	73
Uppsala	9	9	3	0	0	0	0			
Tartu*									6	9

Table 1. Number of first liver transplantations performed at the individual centers during the last 10 years. *Data from Tartu are only included from the time Estonia joined Scandiatransplant

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Copenhagen	3	4	9	4	3	6	3	9*	5	4
Gothenburg	11	19	16	4	9	8	8	17	10	3
Helsinki	6	3	4	4	5	3	7	7	6	6
Oslo	13	12	8	11	14	11	14	12	17	8
Stockholm	3	1	8	5	7	8	8*	7	5	4
Uppsala	1	0	0	0	0	0	0	0	0	0
Tartu**									0	1

Table 2. Total number of re-transplantations performed at the individual centers during the last 10 years. * = 1 pts in 2015 and one in 2016 received their first graft outside SCTP **Data from Tartu are only included from the time Estonia joined Scandiatransplant

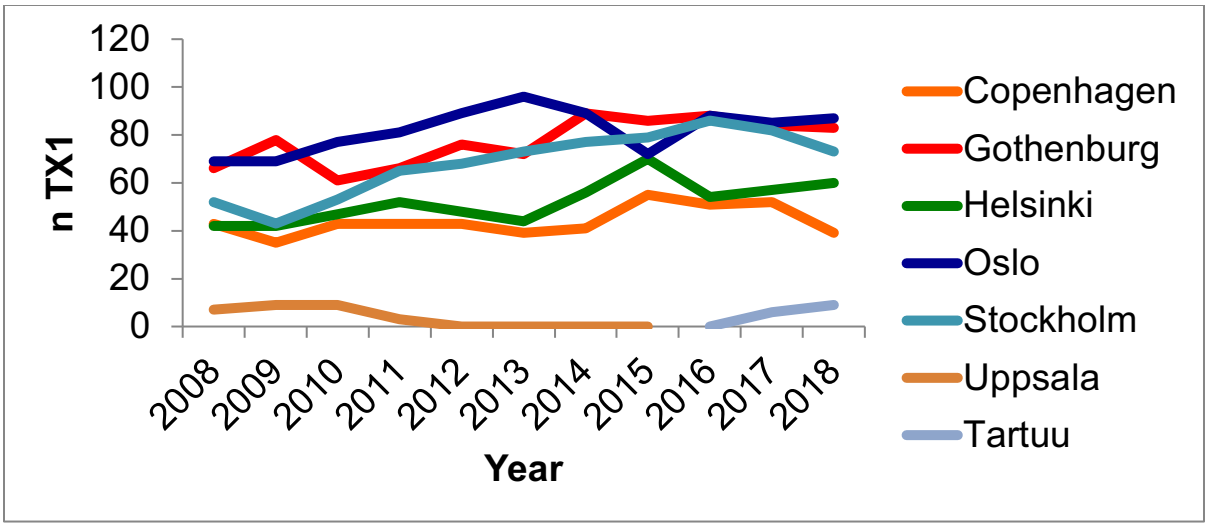

Figure 2. Number of first liver transplantations performed at the Nordic and Estonian centers that are currently performing liver transplantations.

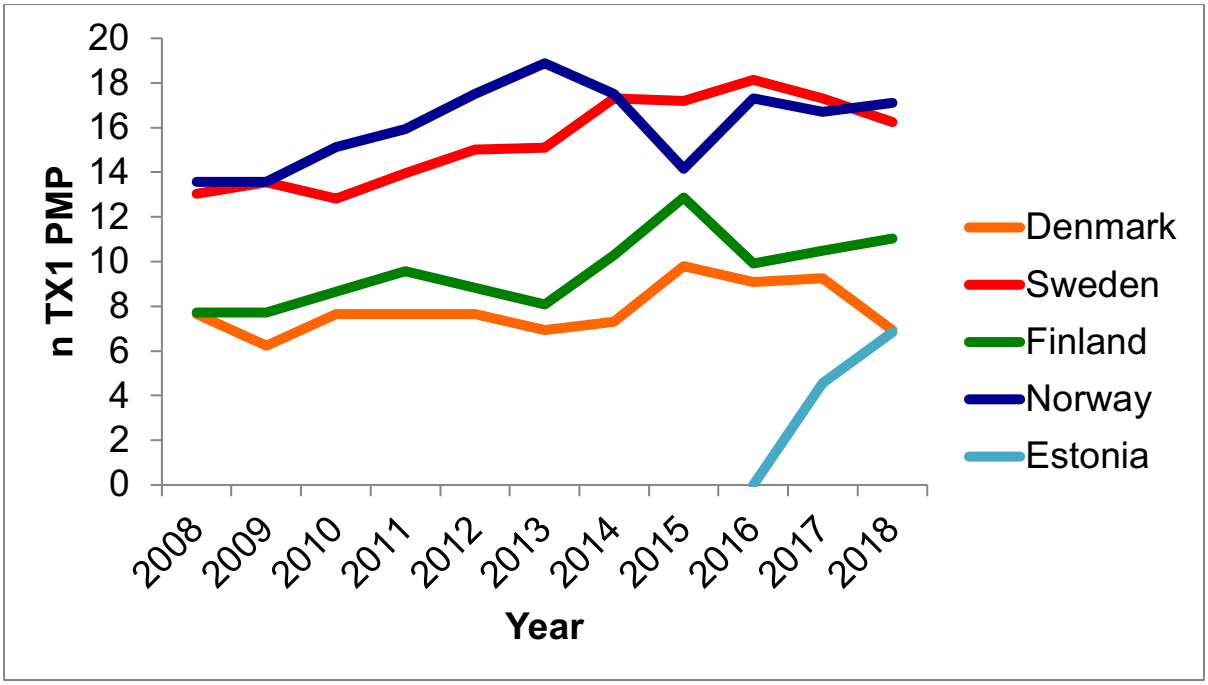

Figure 3. Number of first liver transplantations performed in the Scandiatransplant countries according to the country's population. PMP, per million population.

4. The waiting list 2018

In 2018, a total of 380 patients were entered on the waiting list for a first liver transplant (Table 3), this is a decrease from the 389 entered in 2017 (Figure 4). Twenty-three of the patients entered in 2018 were listed as highly urgent.

Active on waiting list	Deceased donor	Living donor	Dead	Permanent withdrawal
83	269	2	9	17

Table 3. *Patients entering the waiting list in 2018 classified by outcome as of December 31st 2018.*

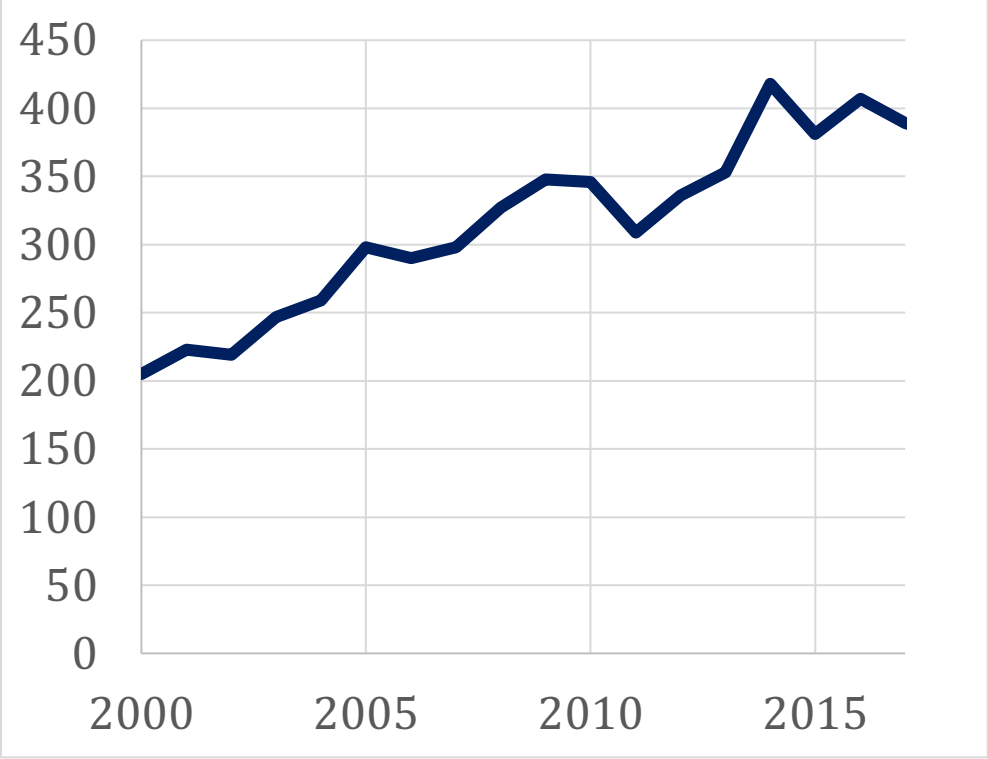

Figure 4. Number of patients entering the waiting list from 2000-2018.

The number of deaths among patients listed in 2018 for a first liver transplant was 9 (Denmark 1, Sweden 4, Finland 0, Norway 3 and Estonia 1). The absolute number of deaths registered on the waiting

list has remained stable since 1990 (Figure 5). When the deaths on the waiting list are evaluated in relation to the total liver transplantation activity in 2018 the relative number of deaths on the waiting list remains low (Figure 6).

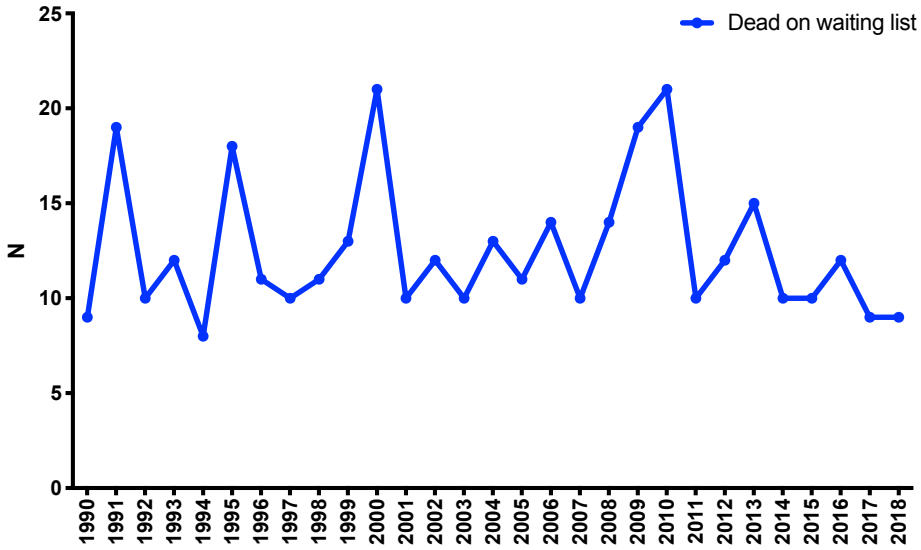

Figure 5. Number of patients registered as dead on the waiting list in the period 1990-2018.

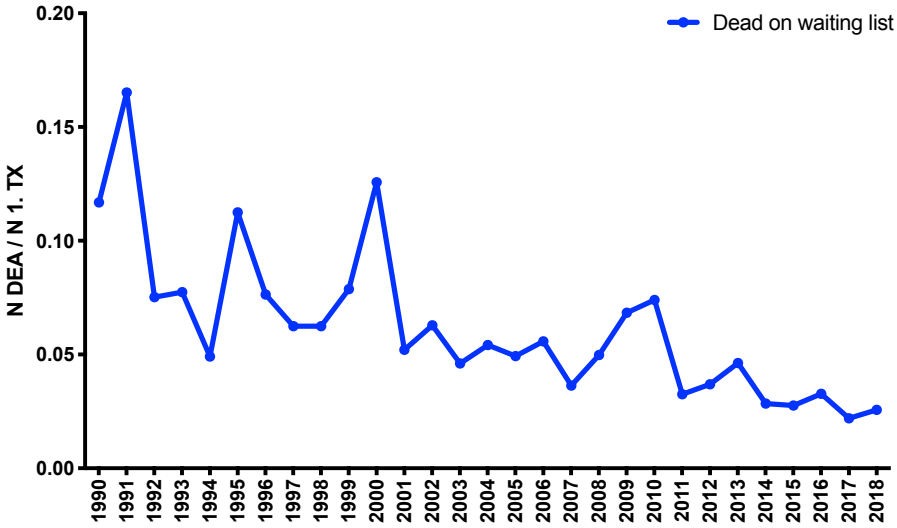

Figure 6. Number of patients registered as dead on the waiting list relative to the total transplantation activity in the period 1990-2018.

The median waiting time in 2018 was 61 days when excluding patients listed for a highly urgent liver transplantation. The differences according to different ABO blood types were as expected (Table 4) with largely similar numbers since 2010 (Figure 7).

0	A	AB	B
111 (1066)	42 (293)	23.5 (144)	51 (408)

Table 4. Median time on waiting list (days) for patients receiving a first liver allograft in 2018 according to ABO blood type. The number in parenthesis represents the maximum waiting time for the indicated blood type in 2018. (Patients listed as highly urgent are excluded from the calculations.)

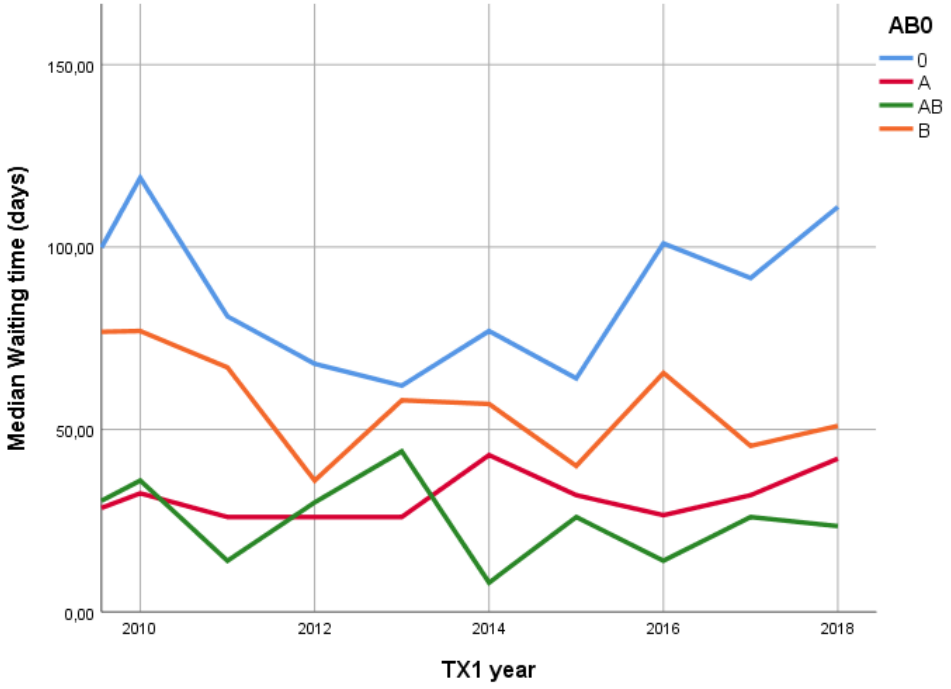

Figure 7. Median waiting time for first liver transplantation according to ABO blood type for 2010-2018. (Patients listed as highly urgent are excluded from the calculations.)

Finland had the lowest and Tartu the longest waiting time in 2018 (Table 5). The waiting times are markedly higher than previous years (Figure 8), although low compared to other transplant programs.

Copenhagen	Gothenburg	Helsinki	Oslo	Stockholm	Tartu
114 (1066)	73 (841)	33 (168)	62 (491)	80 (828)	119 (235)

Table 5. Median time on waiting list (days) for patients receiving a first liver allograft in 2018 according to transplantation center. The number in parenthesis represents the maximum waiting time for the indicated center in 2018. (Patients listed as highly urgent are excluded from the calculations.)

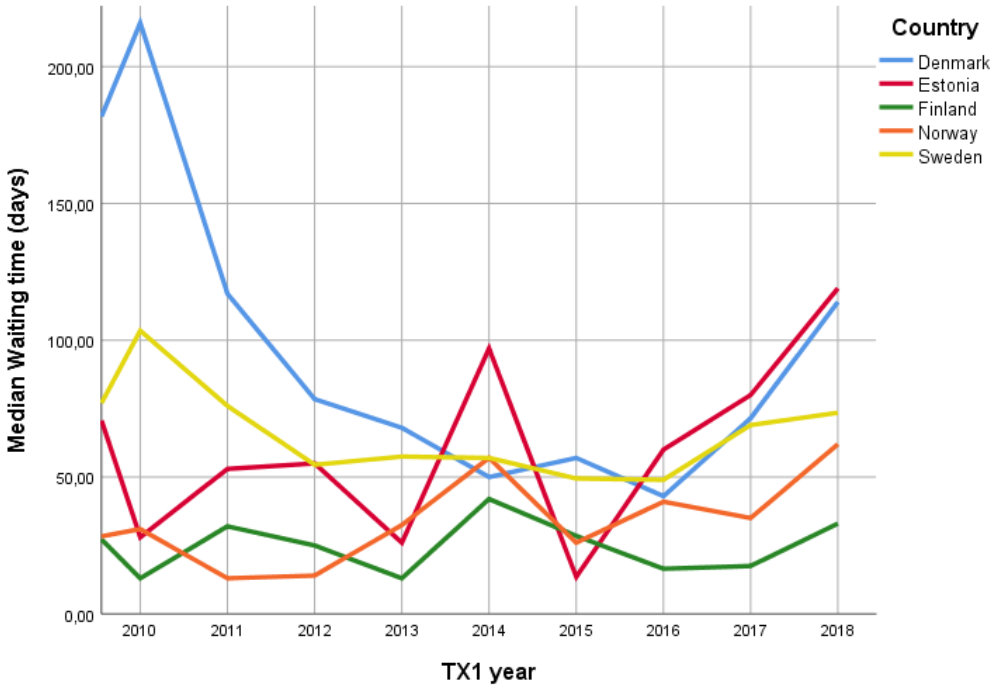

Figure 8. Median waiting time for first liver transplantation according to country for 2010-2018. (Patients listed as highly urgent are excluded from the calculations.)

5. Age of recipients and donors

The mean age of adult liver recipients (>18 years, first liver transplantation) in 2018 was 54.1 years. Mean age of children (<18 years, first liver transplantation) in 2018 was 6.3 years. Since 1990 the proportion of recipients >60 years of age at the first transplantation has gradually increased and in 2018 35% of the patients were above 60 years of age (Figure 9). The mean age of the donors has remained stable since 2010 with a median age of 58.0 years in 2018 (Figure 10).

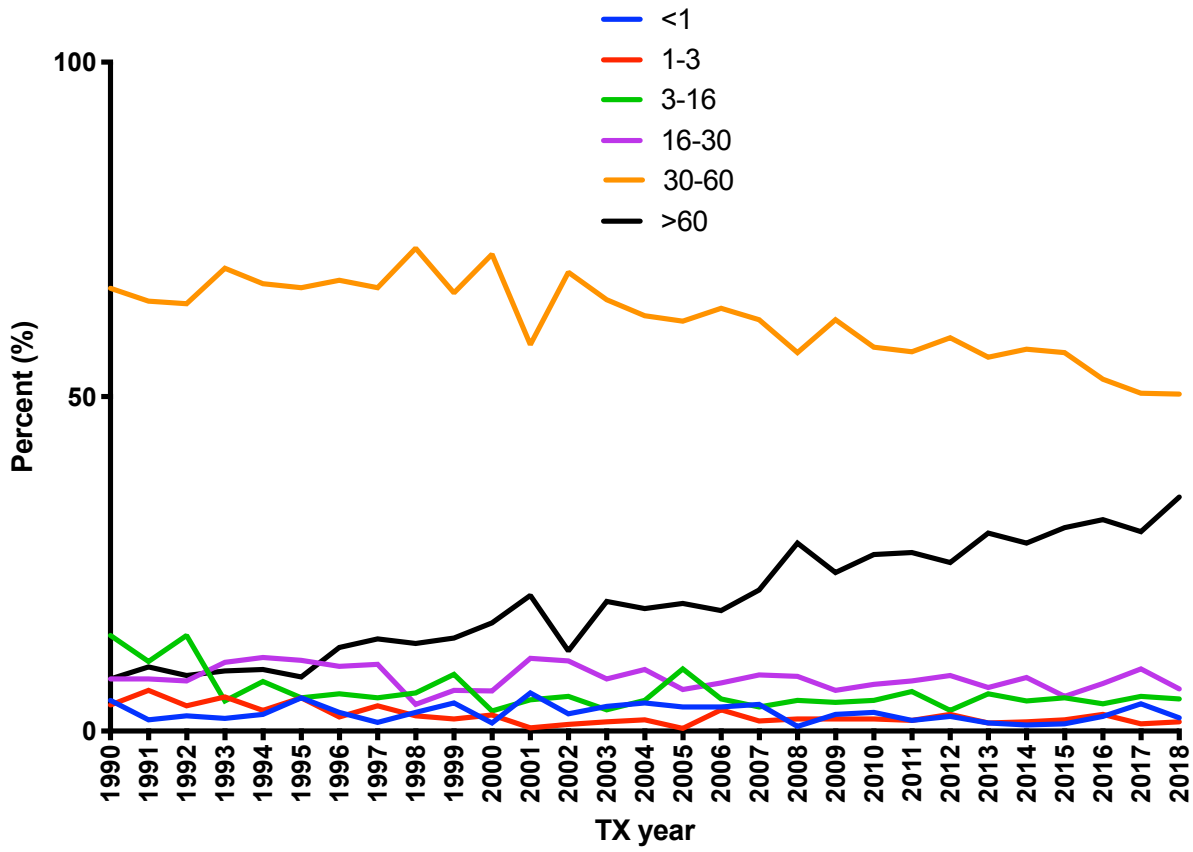

Figure 9. Proportion of liver transplants in the indicated age groups.

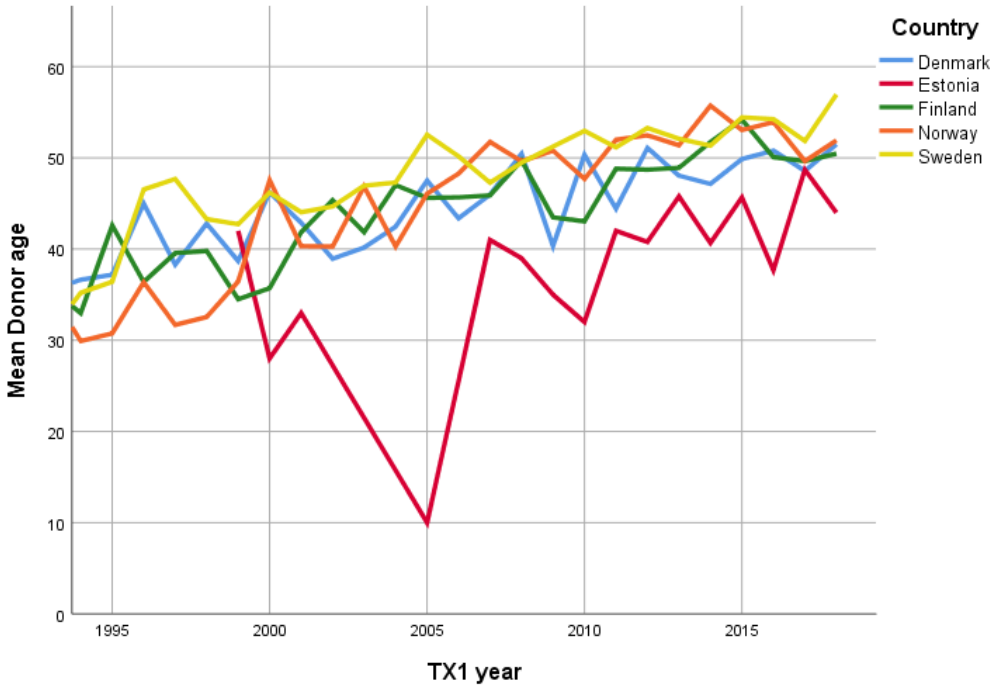

Figure 10. Mean age of donors utilized in the indicated years stratified for the different Nordic countries.

6. Diagnoses

In 2018, hepatocellular carcinoma and primary sclerosing cholangitis were the leading indications for liver transplantation in the Nordic countries (Table 6). Of the patients listed for transplantation with a primary diagnosis of hepatocellular carcinoma (HCC) in 2018 28% were also anti-HCV positive. During the last 3-4 years the percentage of patients listed for transplantation with a diagnosis of HCV cirrhosis has dramatically declined (Figure 11). This decline coincides with the introduction of direct acting antiviral treatment.

	1982-90	1991-98	1999-03	2004-08	2009-13	2014-18	2018
Hepatocellular carcinoma and cirrhosis	10.9 %	5.0 %	5.7 %	8.3 %	14.4 %	17.0 %	17.6 %
Primary sclerosing cholangitis	10.9 %	13.5 %	16.1 %	15.6 %	14.7 %	17.9 %	15.3 %
Alcoholic cirrhosis	1.9 %	9.9 %	11.6 %	11.8 %	11.5 %	12.5 %	13.2 %
Metabolic disease	9.3 %	7.3 %	5.4 %	5.6 %	7.9 %	8.3 %	7.9 %
Primary biliary cirrhosis	22.7 %	12.4 %	7.1 %	7.3 %	5.7 %	4.7 %	6.8 %
Acute liver failure - other	8.7 %	9.7 %	6.9 %	6.0 %	5.0 %	5.9 %	6.6 %
Cirrhosis - unknown	0.6 %	3.1 %	2.3 %	3.7 %	6.2 %	5.5 %	4.7 %
Autoimmune cirrhosis	2.8 %	3.5 %	3.7 %	4.8 %	4.1 %	4.7 %	4.5 %
Post hepatitis C cirrhosis		4.8 %	9.2 %	10.8 %	10.3 %	4.1 %	2.9 %
Polycystic disease	0.3 %	1.2 %	1.3 %	1.6 %	1.5 %	2.4 %	2.4 %
Extrahepatic biliary atresia	6.8 %	5.0 %	4.6 %	3.7 %	2.3 %	2.4 %	2.1 %
Secondary liver tumors	0.9 %	0.3 %	0.9 %	2.0 %	1.7 %	1.9 %	2.1 %
Acute liver failure - toxic	0.6 %	2.9 %	4.9 %	4.1 %	3.0 %	2.5 %	1.8 %
Budd-chiari	1.6 %	2.0 %	1.4 %	0.9 %	1.1 %	0.8 %	1.6 %
Acute liver failure - viral	1.2 %	2.2 %	1.5 %	0.7 %	2.0 %	0.8 %	1.1 %
Post hepatitis B cirrhosis	0.9 %	2.7 %	3.4 %	2.2 %	1.2 %	1.1 %	1.1 %
Post hepatitis D cirrhosis		0.1 %		0.1 %	0.6 %	0.6 %	1.1 %
Others	19.9 %	14.2 %	14.0 %	10.6 %	6.7 %	6.8 %	7.4 %

Table 6. *Diagnoses of patients listed for a first liver transplantation in 2018 compared with previous years. In 2018 28% of HCC patients listed for a first liver transplantation were anti-HCV positive.*

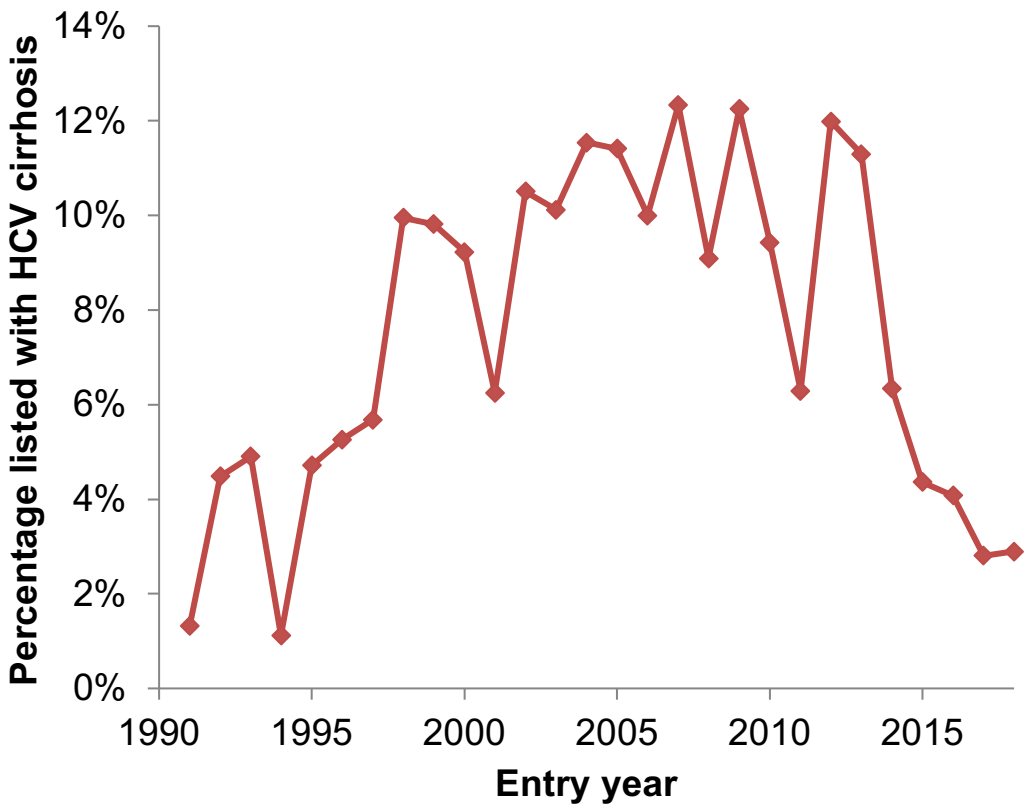

Figure 11. Percentage of patients listed with HCV cirrhosis from 1990-2018.

7. Patient and liver graft survival

When looking at 5-years intervals, patient survival (defined as time from the first liver transplantation until death) and graft survival (defined as time from the first liver transplantation until death or re-transplantation) were dramatically improving over the first years of the Nordic liver transplantation programs (Figures 12 and 13). It is now evident that there is a further increase in the observed survival also in the most recent 5-year period. There are notable differences in the long-term patient and graft survival for different indications for transplantation (Figures 14, 15 and Table 7). The survival following retransplantation is reduced compared to the primary transplantation, this is particularly evident in during the first months after the transplantation (Figure 16). Similar to the survival following the primary transplantation, the survival following retransplantation is

markedly better in the recent time-periods compared to the start of the program. However, a further improvement in the most recent period is not seen. In an intention-to-treat analysis analysing survival from the listing for transplantation, the survival is lower but encompasses all events following listing and gives an indication of the performance of the program (Figure 17).

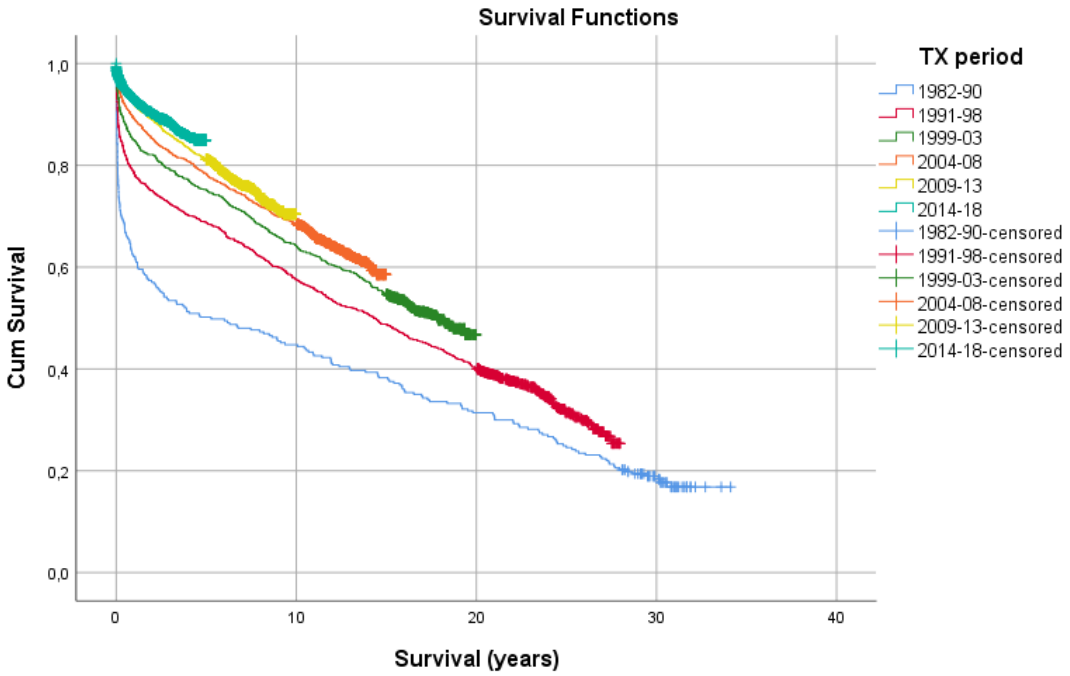

Figure 12. Kaplan-Meier patient survival curve for patients receiving a first liver allograft in the indicated time periods.

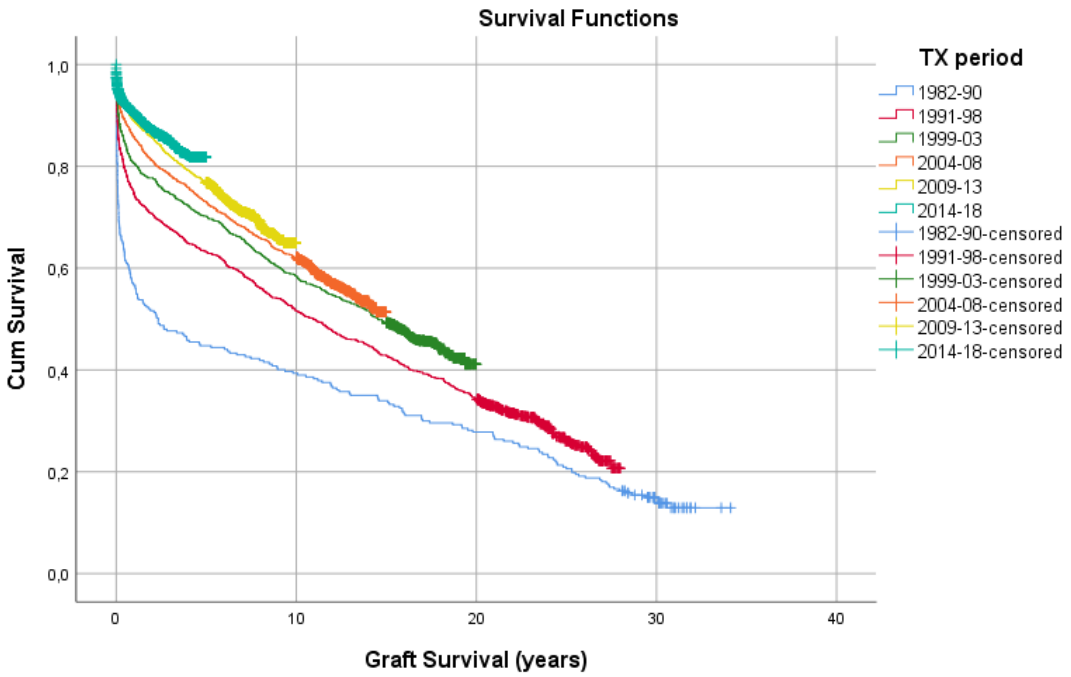

Figure 13. Kaplan-Meier graft survival curve for patients receiving a first liver allograft in the indicated time periods.

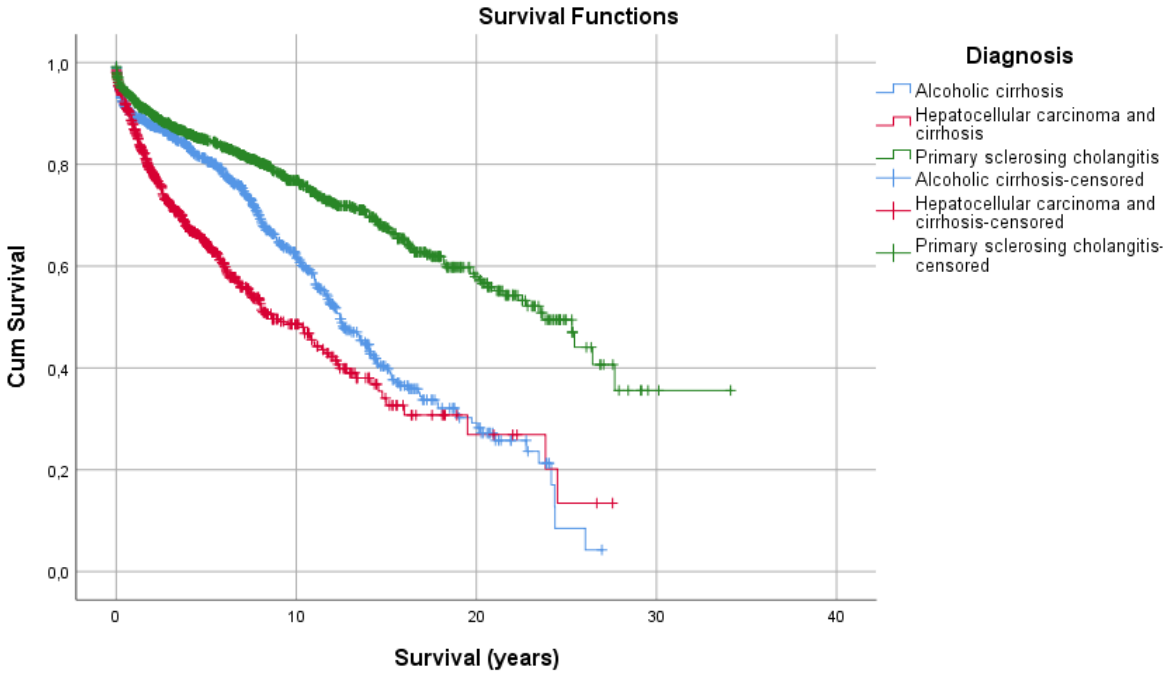

Figure 14. Kaplan-Meier patient survival curve for patients receiving a first liver allograft stratified for the three most common primary diagnoses.

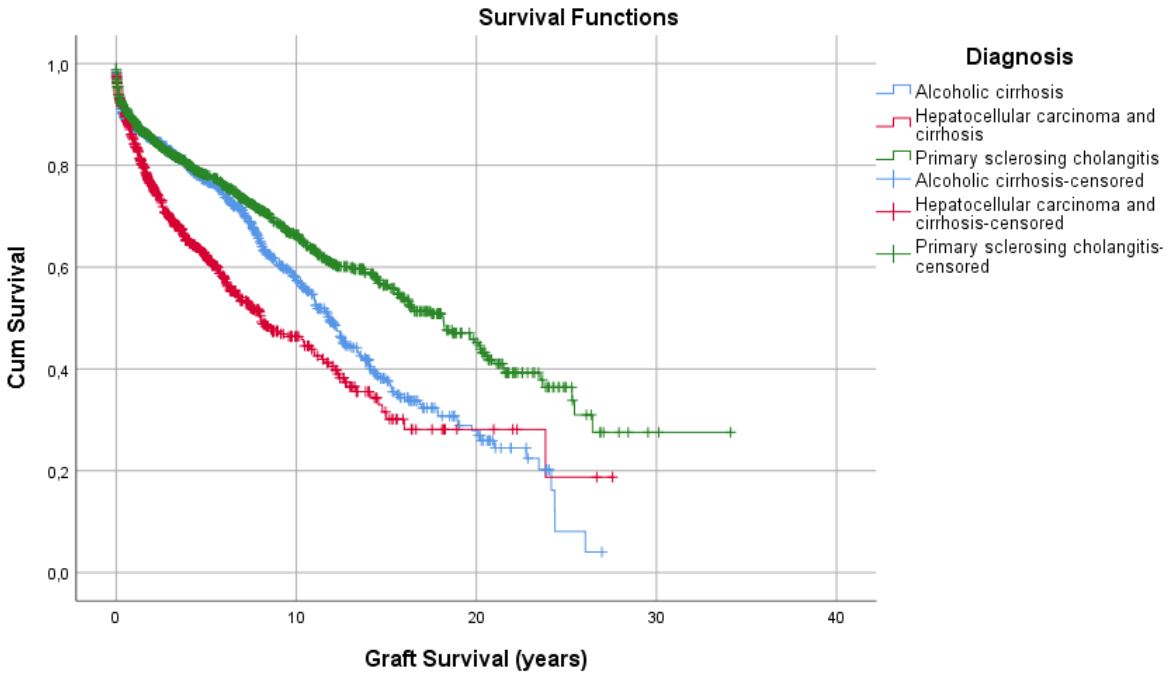

Figure 15. Kaplan-Meier graft survival curve for patients receiving a first liver allograft stratified for the three most common primary diagnoses.

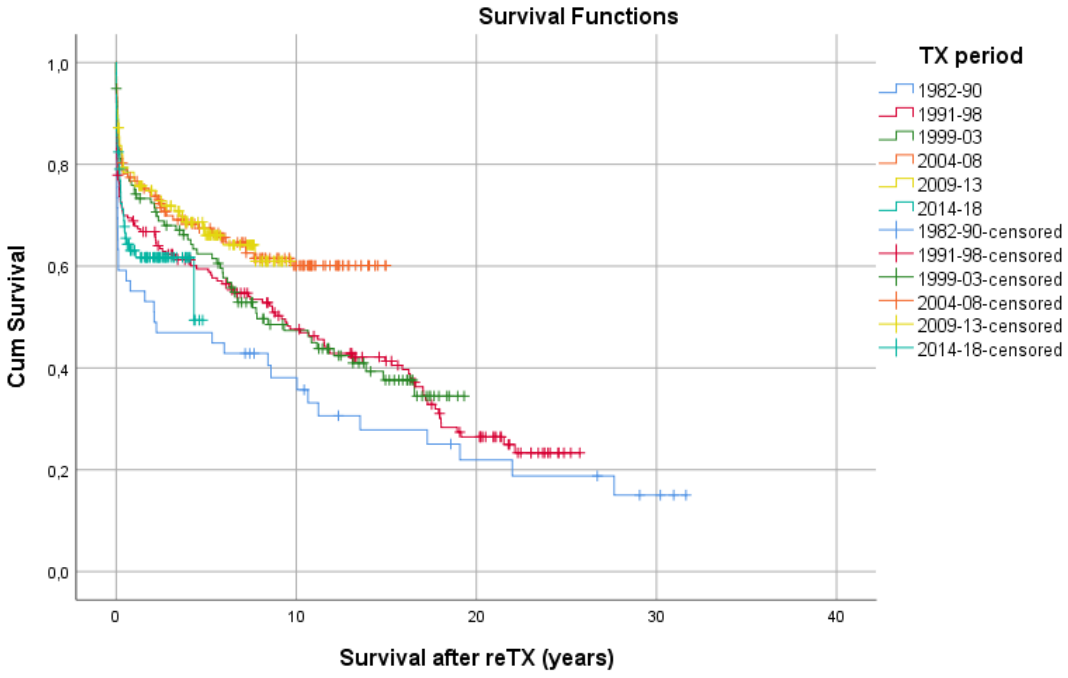

Figure 16. Kaplan-Meier patient survival curve for patients following retransplantation in the indicated time periods.

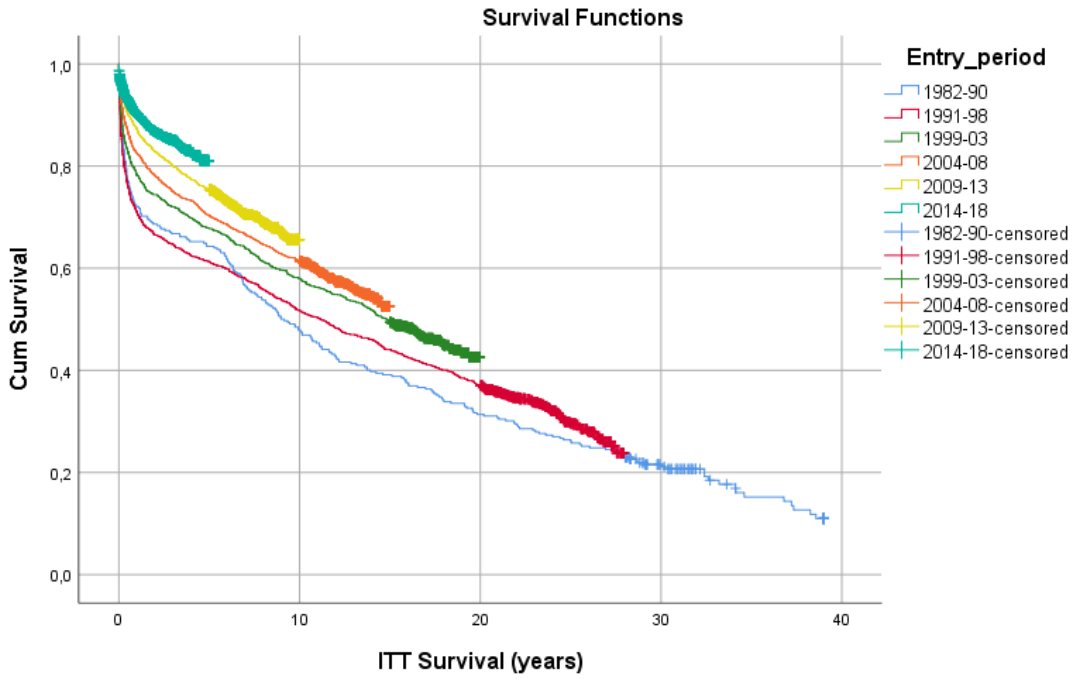

Figure 17. Kaplan-Meier patient intention-to-treat survival curve following listing for transplantation.

	Median age	1-year survival (%)	5-year survival (%)
Hepatocellular carcinoma and cirrhosis	60.9	94 %	74 %
Primary sclerosing cholangitis	43.9	98 %	92 %
Alcoholic cirrhosis	57.4	94 %	87 %
Metabolic disease	50.2	94 %	94 %
Primary biliary cirrhosis	56.5	93 %	83 %
Cirrhosis - unknown	55.5	92 %	83 %
Autoimmune cirrhosis	50.6	94 %	88 %
Post hepatitis C cirrhosis	54.2	90 %	75 %
Polycystic disease	53.9	97 %	94 %
Extrahepatic biliary atresia	1.1	88 %	85 %
Listed as highly urgent	42.8	83 %	80 %

Table 7. *Age at transplant and survival for the patients listed 2010-2018 for the ten most common diagnoses and those listed as highly urgent*

8. Maintenance of the registry

There are differences between each center in terms of how extensively data are entered into the NLTR. Diagnosis information, waiting list/transplantation status and survival data for all patients are now complete for 2018. I am extremely grateful for dedicated follow-up provided by the transplant coordinators upon my requests during quality control. In Oslo, I particularly want to thank Stein Foss and Monika Olofsson, in Gothenburg Ulla Nyström, in Stockholm Marie Tranäng, in Copenhagen Mette Gottlieb, in Helsinki Leena Toivonen and in Tartu Virge Pall has taken care of the registry in the first two years. Quality control of the content of NLTR is a continuous priority, and a particular emphasis is put into ensuring integrity of the survival data, including cause of death. The remainder of the registry must be maintained at a level set at the discretion of each individual center and contact person. The export of data from NLTR to ELTR is now ready and only regulatory approvals at some centers are pending. This will save the coordinators at the different centers a lot of redundant work by avoiding entry of data into two registries. In 2018 the scientific output from the registry was good with a range of papers utilizing the special characteristics of the Scandiatransplant program.

9. Acknowledgements - financial support

The NLTR received no financial support in 2018. The maintenance of the Oracle system has been performed by Scandiatransplant. We are extremely grateful for the help and support from Ilse Duus Weinreich and the rest of the Scandiatransplant team in Aarhus. Without their assistance, it would very simply not have been possible to maintain the registry and I sincerely hope their efforts are recognized by the NLTG and Scandiatransplant.

10. Organization and data ownership

The registry (software) is the property of Scandiatransplant. The data in the registry are the property of the hospitals represented in the Nordic Liver Transplantation Group. Utilization of data in research projects should be censored by the latter and need to comply with national guidelines for research ethics and data handling. Co-authorships for publications from research projects should be allocated according to the Vancouver guidelines, this includes presentations of data at conferences. The quality statistics of the transplantation activity presented in this report must not be used in other contexts without permission from the Nordic Liver Transplantation Group.

11. Publications based on the NLTR

Full length articles 1990-2018:

1. Keiding S, Ericzon BG, Eriksson S, Flatmark A, Hockerstedt K, Isoniemi H, Karlberg I, Keiding N, Olsson R, Samela K, Schrumpf E. Survival after liver transplantation of patients with primary biliary cirrhosis in the Nordic countries. Comparison with expected survival in another series of transplantations and in an international trial of medical treatment. Scand J Gastroenterol 1990; 25:11-8

2. Hockerstedt K, Ericzon BG, Eriksson LS, Flatmark A, Isoniemi H, Karlberg I, Keiding N, Keiding S, Olsson R, Samela K. Survival after liver transplantation for primary biliary cirrhosis: use of prognostic indices for comparison with medical treatment. Transpl Proc 1990; 22:1499-500

3. Hockerstedt K, Isoniemi H, Ericzon BG, Broome U, Friman S, Persson H, Bergan A, Schrumpf E, Kirkegaard P, Hjortrup A. Is a 3-day waiting list appropriate for patients with acute liver failure?

Transpl Proc 1994;26:1786-7 4. Bjøro K, Friman S, Höckerstedt K, Kirkegaard P, Keiding S, Schrumpf E, Olausson M, Oksanen A, Isoniemi H, Hjortrup A, Bergan A, Ericzon BG. Liver transplantation in the Nordic countries, 1982-1998: Changes of indications and improving results. Scand J Gastroenterol 1999;34:714-722

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7. Ericzon BG, Bjøro K, Höckerstedt K, Hansen B, Olausson M, Isoniemi H, Kirkegaard P, Broome U, Foss A, Friman S. Time to request AB0-identity when transplanting for fulminant hepatic failure? Transpl Proc 2001;33:3466-7 8. Leidenius M, Broome U, Ericzon B-E, Friman S, Olausson M, Schrumpf E, Höckerstedt K. Hepatobiliary carcinoma in primary sclerosing cholangitis: a case control study. J Hepatol 2001;34:792-8.

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10. Brandsæter B , K Höckerstedt, BG Ericzon, S Friman, P Kirkegaard, H Isoniemi, Foss A, Olausson M, Hansen B, Bjøro K: Outcome following listing for liver transplantation due to fulminant hepatic failure in the Nordic countries. Liver Transplantation 2002;8:1055-62

11. Bjøro K, Ericzon BG, Kirkegaard P, Höckerstedt K, Söderdahl G, Olausson M, Foss A, Schmidt LE, Brandsæter B, Friman S. Liver transplantation for fulminant hepatic failure: impact of donor-recipient ABO-matching on the outcome. Transplantation 2003; 75:347-53

12. Brandsæter Bjørn, Broomé Ulrika, Isoniemi Helena, Friman Styrbjörn, Hansen Bent, Schrumpf Erik, Oksanen Antti, Ericzon Bo-Göran, Höckerstedt Krister, Mäkisalo Heikki, Olsson Rolf, Olausson Michael, Kirkegaard Preben, Bjøro Kristian. Liver transplantation for primary sclerosing cholangitis in the Nordic countries: outcome after acceptance to the waiting list. Liver Transpl. 2003;9:961-9.

13. Brandsaeter B, Friman S, Broome U, Isoniemi H, Olausson M, Backman L, Hansen B, Schrumpf E, Oksanen A, Ericzon BG, Hockerstedt K, Makisalo H, Kirkegaard P, Bjoro K.Outcome following liver transplantation for primary sclerosing cholangitis in the Nordic countries. Scand J Gastroenterol. 2003;38:1176-83.

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17. Melum E, Schrumpf E, Bjøro K. Liver TX for hepatitis C

cirrhosis in a low prevalence population: risk factors and status at evaluation. Scand J Gastroenterol. 2006;41:592-6.

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