

The Nordic Liver Transplant Registry (NLTR)

Annual report 2017

Report prepared by Espen Melum June 2018

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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 June 2018. 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 2017

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 also included. All data are stored securely at ScandiTransplant in Århus (www.scandiatransplant.org).

Up to December 31st 2017, data from a total of 7619 patients had been entered into NLTR. Of these, 6649 patients had received a first liver graft, 679 (10.2%) had been transplanted more than once, and 101 (1.5%) had been transplanted more than twice. Of the 679 patients receiving a second liver graft 7 had received their first graft outside of the ScandiTransplant area. A total of 173 living donor transplantations had been performed. Children below 16 years constituted 684 (10.3%) of the transplanted patients in the registry.

3. Transplantation activity 2017

The total number of patients who received a first liver graft in 2017

was 366 (Figure 1). Of these, 10 were combined liver-kidney transplantations, 2 were combined liver-lung and 2 were multivisceral. Of the first liver transplantations performed in 2017 5 were living donor transplantations and 2 were domino transplantations. Four of the living donor transplantations were performed in Stockholm and one in Gothenburg. In addition, 43 re-transplantations were performed (Table 2). The total number of liver transplantations were 409 including the transplantations performed in Estonia, for the countries that were part of ScandiTransplant also in 2016 the total number is 403 which is a reduction of 3.8% compared to 2016. The relative number of re-transplantations has remained stable in the recent years (Figure 1).

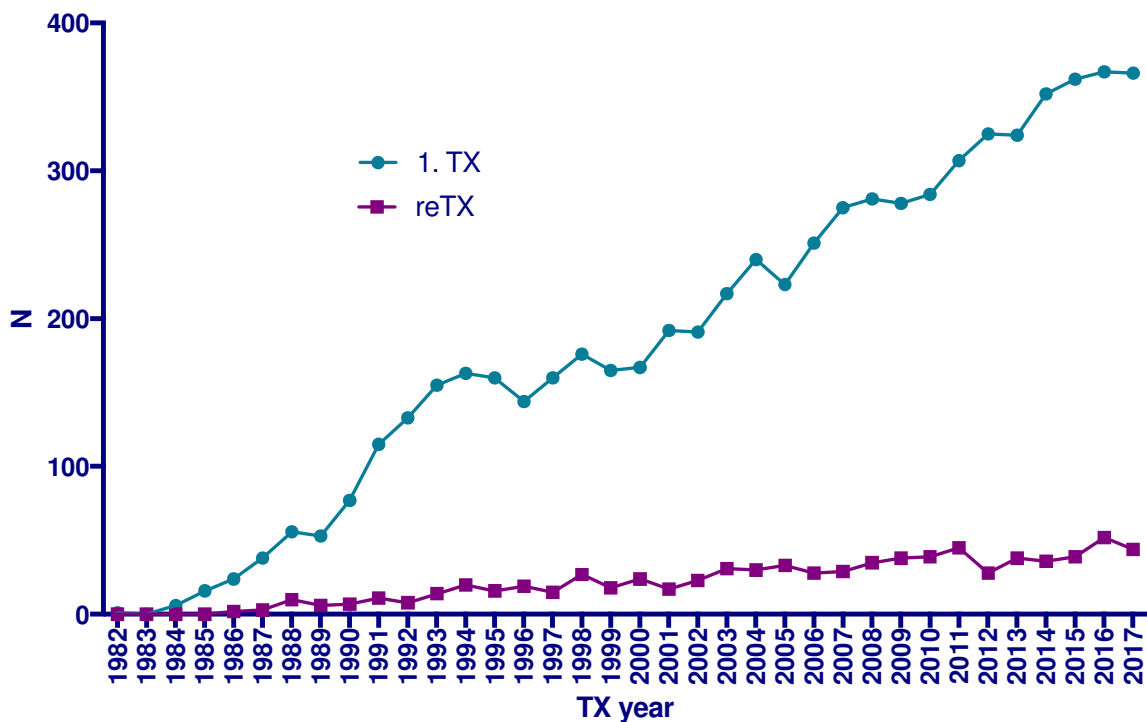


Figure 1. Number of patients receiving a liver allograft 1982-2017. The turquoise line represents the number of patients receiving a first liver graft while the purple line represents the total number of re-transplantations.

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Copenhagen	43	37	43	42	44	39	41	55	51	52
Gothenburg	66	78	61	67	75	72	89	86	88	84
Helsinki	42	42	47	52	48	44	56	70	54	57
Oslo	69	69	77	81	89	96	89	72	88	85
Stockholm	52	43	53	65	69	73	77	79	86	82
Uppsala	11	10	3	0	0	0	0	0	0	0
Tartu										6

Table 1. Number of first liver transplantations performed at the individual centers during the last 10 years.

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Copenhagen	1	3	4	9	4	3	6	3	9*	5
Gothenburg	10	11	19	16	4	9	8	8	17	10
Helsinki	5	6	3	4	4	5	3	7	7	6
Oslo	10	13	12	8	11	14	11	14	12	17
Stockholm	6	3	1	8	5	7	8	8*	7	5
Uppsala	2	1	0	0	0	0	0	0	0	0
Tartu										0

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

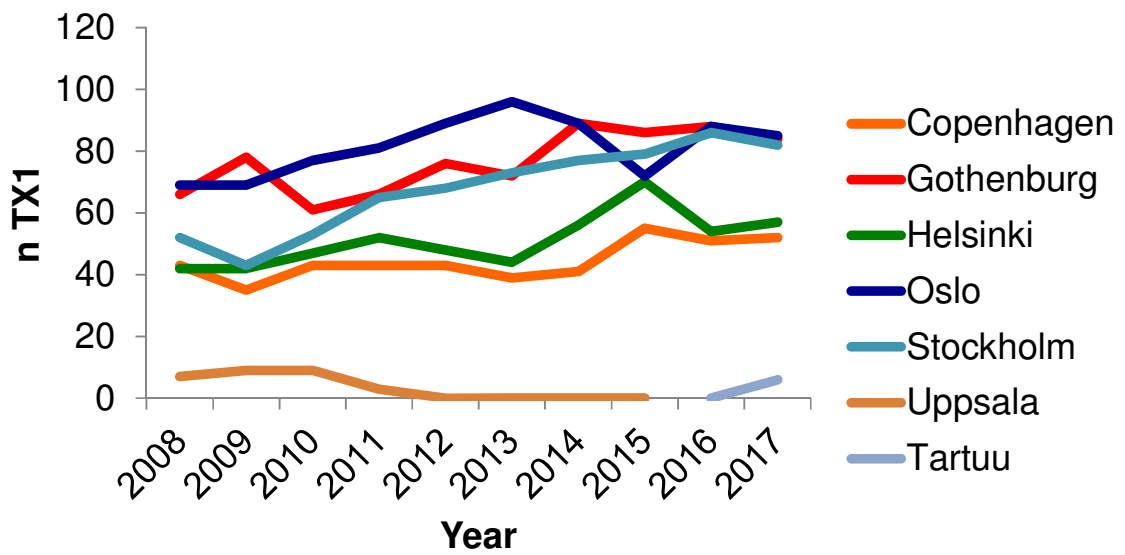


Figure 2. Number of first liver transplantations performed at the Nordic and Estonian centers that are currently performing liver transplantations.

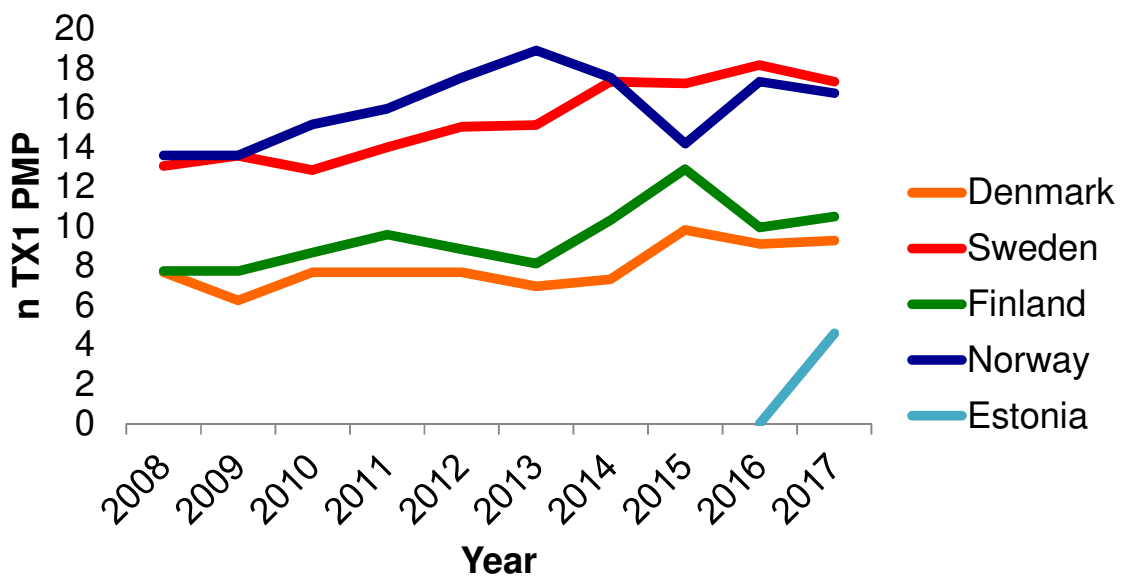


Figure 3. Number of first liver transplantations performed in the Scandi-transplant countries according to the country's population. PMP, per million population.

4. The waiting list 2017

In 2017, a total of 389 patients were entered on the waiting list for a first liver transplant in 2017 (Table 3), this is a decrease from the 407 entered in 2016 (Figure 4). Twenty-seven of the patients entered in 2017 were listed as highly urgent.

Active on waiting list	Deceased donor	Living donor	Dead	Permanent withdrawal
83	280	4	9	13

Table 3. Patients entering the waiting list in 2017 classified by outcome as of December 31st 2017.

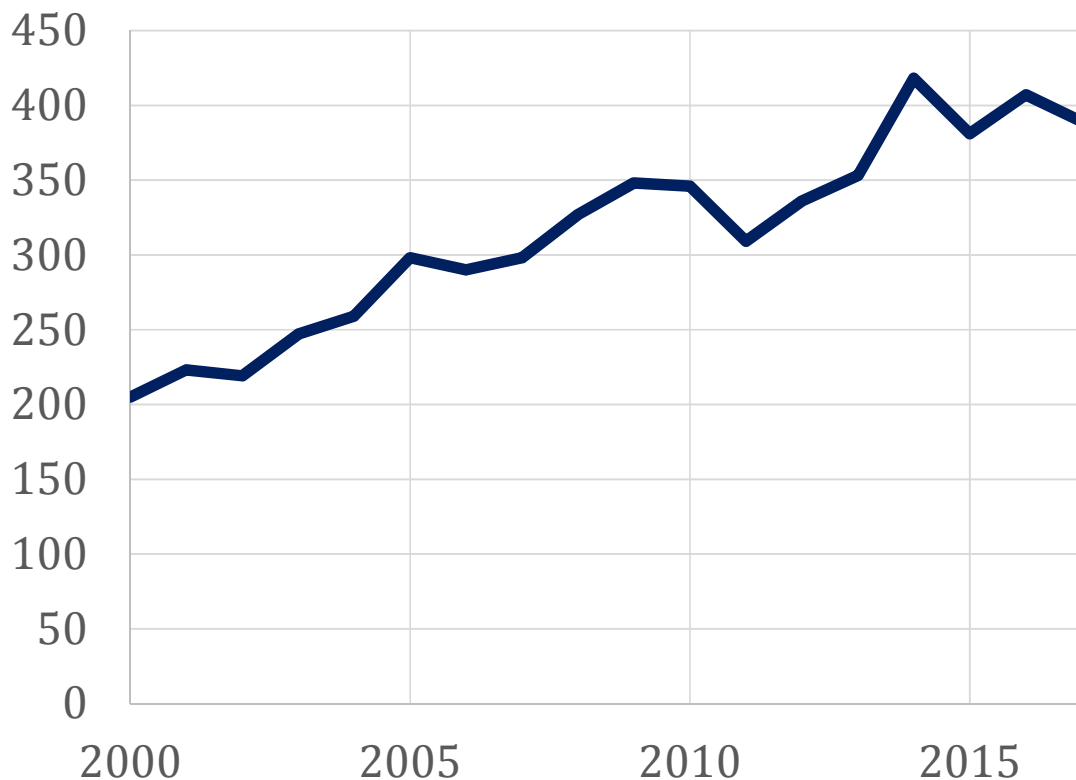


Figure 4. Number of patients entering the waiting list from 2000-2017.

The number of deaths among patients listed in 2017 for a first liver transplant was 9 (Denmark 0, Sweden 4, Finland 1, 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 2017 had the lowest ever number of relative deaths (Figure 6).

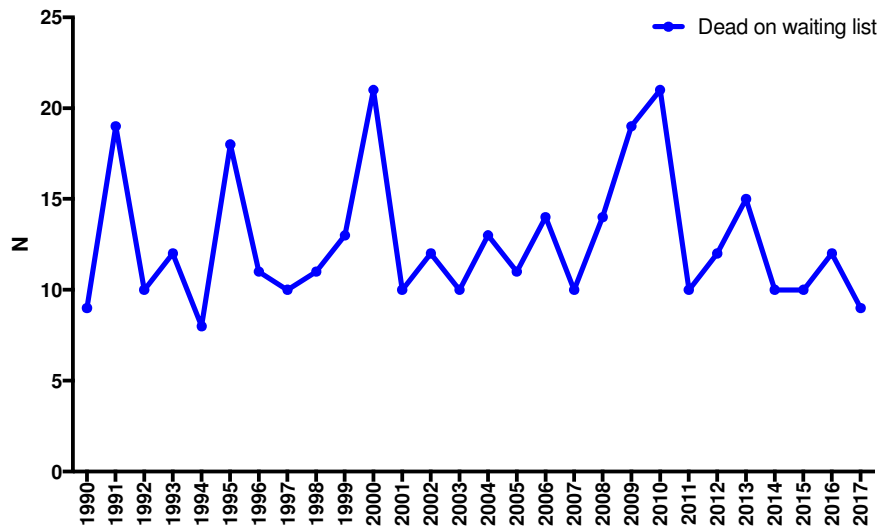


Figure 5. Number of patients registered as dead on the waiting list in the period 1990-2017.

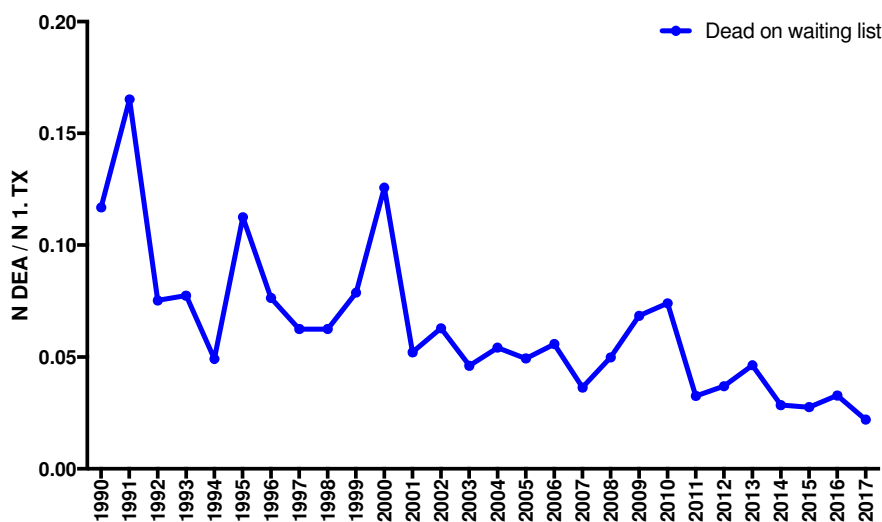


Figure 6. Number of patients registered as dead on the waiting list relative to the total transplantation activity in the period 1990-2017.

The median waiting time in 2017 was 47 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 2000 (Figure 7).

O	A	AB	B
92 (2379)	31.5 (347)	26 (158)	45.5 (544)

Table 4. Median time on waiting list (days) for patients receiving a first liver allograft in 2017 according to ABO blood type. The number in parenthesis represents the maximum waiting time for the indicated blood type in 2017. (Patients listed as highly urgent are excluded from the calculations.)

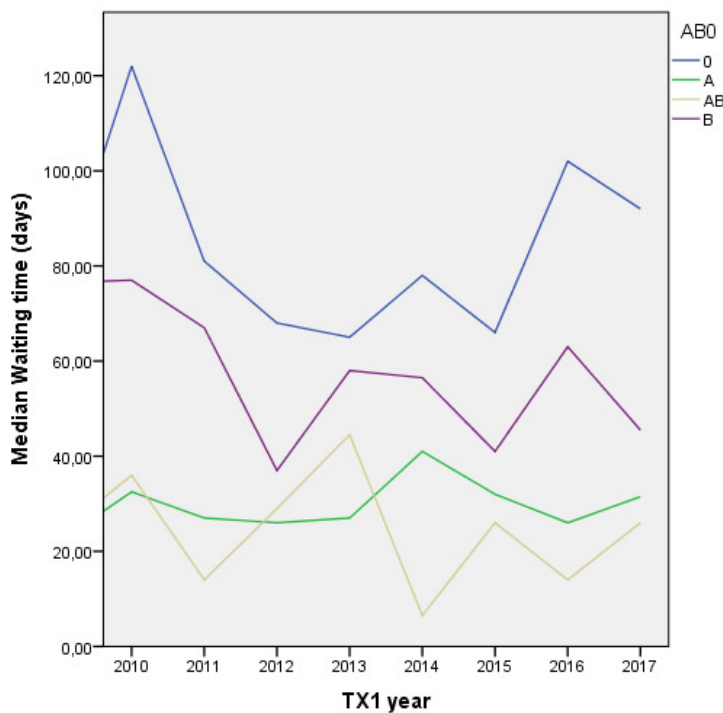


Figure 7. Median waiting time for first liver transplantation according to ABO blood type for 2010-2017. (Patients listed as highly urgent are excluded from the calculations.)

Finland had the lowest waiting time in 2017 while there were only slight differences between the other centers (Table 5). These figures are on the same level as the previous three years (Figure 8).

Copenhagen	Gothenburg	Helsinki	Oslo	Stockholm	Tartu
71.5 (1364)	91.5 (738)	17.5 (215)	35 (2379*)	56.5 (369)	47.0 (308)

Table 5. Median time on waiting list (days) for patients receiving a first liver allograft in 2017 according to transplantation center. The number in parenthesis represents the maximum waiting time for the indicated center in 2017. (Patients listed as highly urgent are excluded from the calculations.) *One patient in Oslo waited for an extended period of time due to simultaneous lung transplantation.

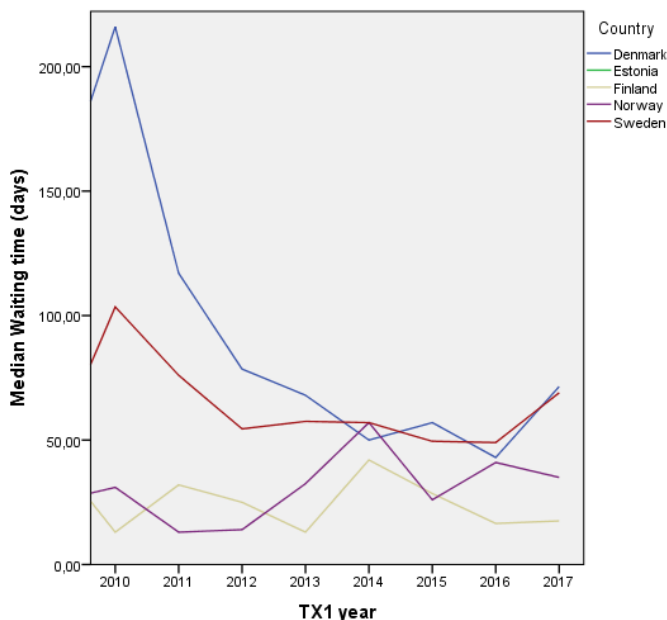


Figure 8. Median waiting time for first liver transplantation according to country for 2000-2017. (Patients listed as highly urgent are excluded from the calculations.)

5. Age of recipients and donors

The mean age of adult liver recipients (≥ 16 years, first liver transplantation) in 2017 was 51.6 years. Mean age of children (< 16 years, first liver transplantation) in 2017 was 4.9 years. Since 1990 the proportion of recipients > 60 years of age at the first transplantation has gradually increased (Figure 9). The mean age of the donors has remained steady since 2010 with a small decrease in 2017 (Figure 10).

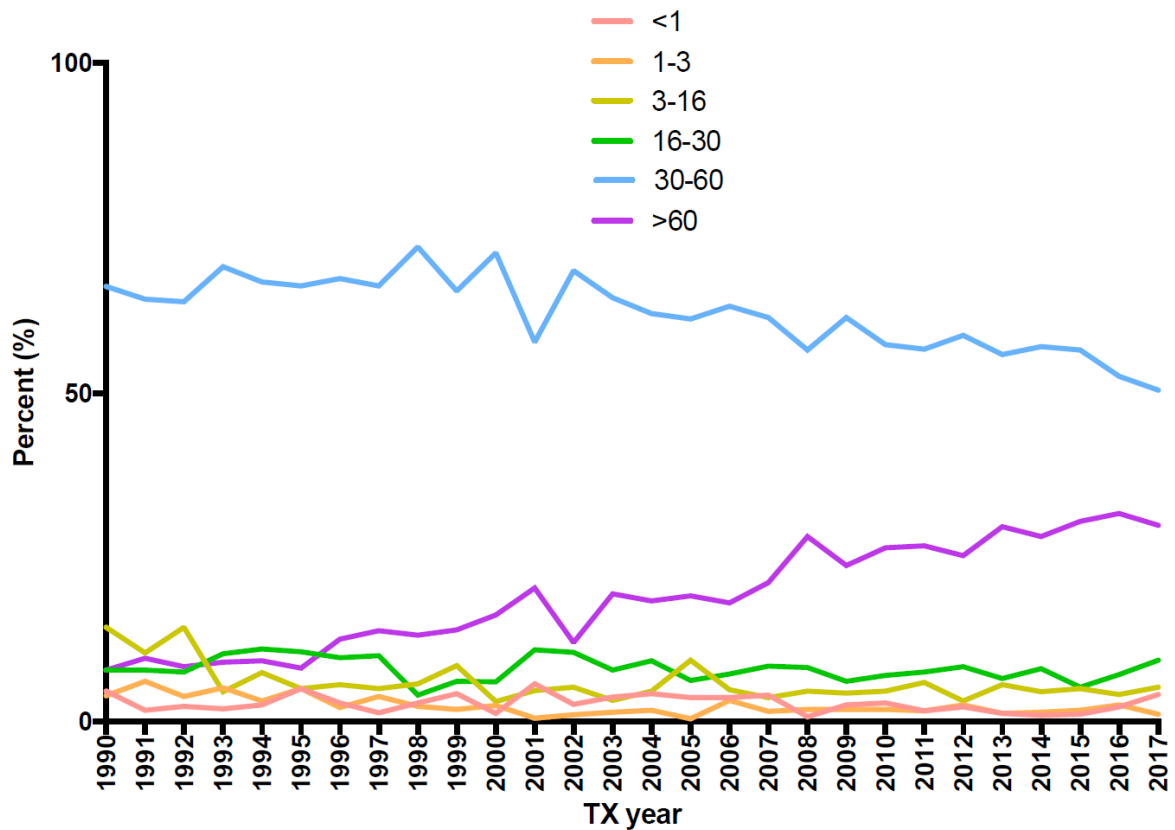


Figure 9. Proportion of liver transplants in the indicated age groups.

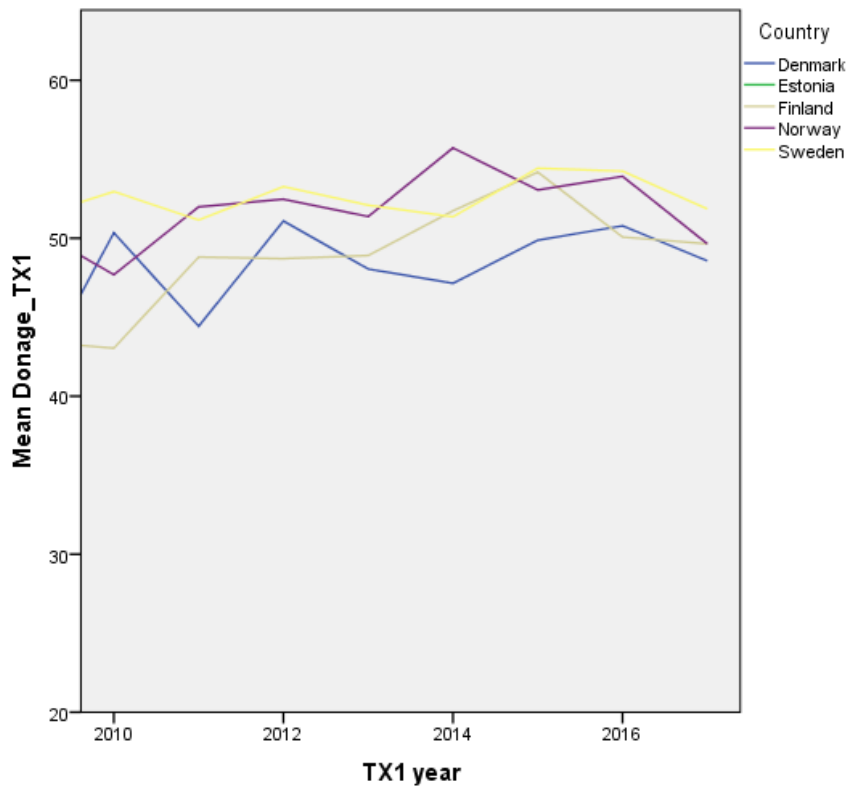


Figure 10. Mean age of donors utilized in the indicated years stratified for the different Nordic countries.

6. Diagnoses

In 2017, primary sclerosing cholangitis and hepatocellular carcinoma 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 2017 40.3% 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 markedly declined (Figure 11). This decline coincides with the introduction of direct acting antiviral treatment.

	1982-90	1991-97	1998-02	2003-07	2008-12	2013-17	2017
Primary sclerosing cholangitis	10.8%	13.7%	15.2%	15.3%	16.3%	17.2%	18.8%
Hepatocellular carcinoma and cirrhosis	10.8%	4.6%	5.9%	8.2%	12.4%	17.5%	16.7%
Alcoholic cirrhosis	1.9%	9.1%	12.3%	11.8%	11.8%	12.2%	14.4%
Metabolic disease	9.6%	7.1%	5.9%	5.2%	7.3%	8.7%	10.3%
Acute liver failure - other	8.7%	10.1%	6.8%	6.6%	5.1%	5.7%	6.4%
Autoimmune cirrhosis	2.8%	3.8%	3.6%	4.6%	3.8%	5.1%	4.4%
Cirrhosis - unknown	0.6%	3.0%	2.6%	2.4%	6.6%	5.9%	3.9%
Extrahepatic biliary atresia	6.8%	5.0%	5.0%	3.9%	2.5%	2.4%	3.1%
Polycystic disease	0.3%	1.2%	1.0%	1.5%	1.6%	2.4%	3.1%
Acute liver failure - toxic	0.6%	2.6%	5.0%	3.9%	3.2%	2.9%	2.8%
Primary biliary cirrhosis	22.6%	13.1%	7.2%	7.3%	6.1%	4.4%	2.3%
Post hepatitis C cirrhosis		4.0%	9.1%	11.1%	9.5%	4.8%	1.8%
Secondary liver tumors	0.9%	0.4%	0.9%	1.4%	2.0%	1.8%	1.8%
Cholangiocarcinoma	1.5%	0.8%	0.9%	0.8%	0.5%	0.4%	1.3%
Biliary tract carcinoma				0.3%	0.8%	0.6%	1.0%
Congenital disease	1.2%	1.2%	1.1%	0.6%	1.2%	0.8%	1.0%
Post hepatitis B cirrhosis	0.9%	2.8%	3.3%	2.7%	1.1%	1.1%	0.8%
Post hepatitis D cirrhosis					0.5%	0.6%	0.8%
Acute liver failure - viral	1.2%	2.4%	1.6%	0.6%	2.0%	0.8%	0.5%
Others	18.6%	15.0%	12.3%	11.8%	5.6%	4.7%	4.9%

Table 6. Diagnoses of patients listed for a first liver transplantation in 2017 compared with previous years. In 2017 40.3% of HCC patients listed for a first liver transplantation were anti-HCV positive.

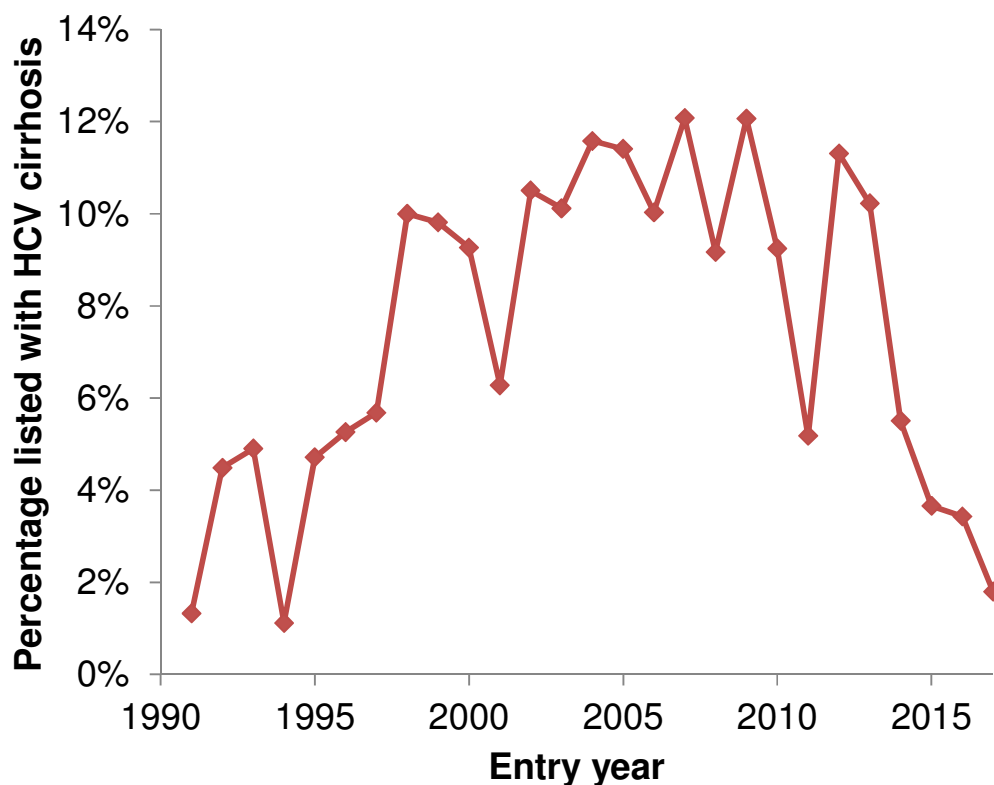


Figure 11. Percentage of patients listed with HCV cirrhosis from 1990-2017.

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).

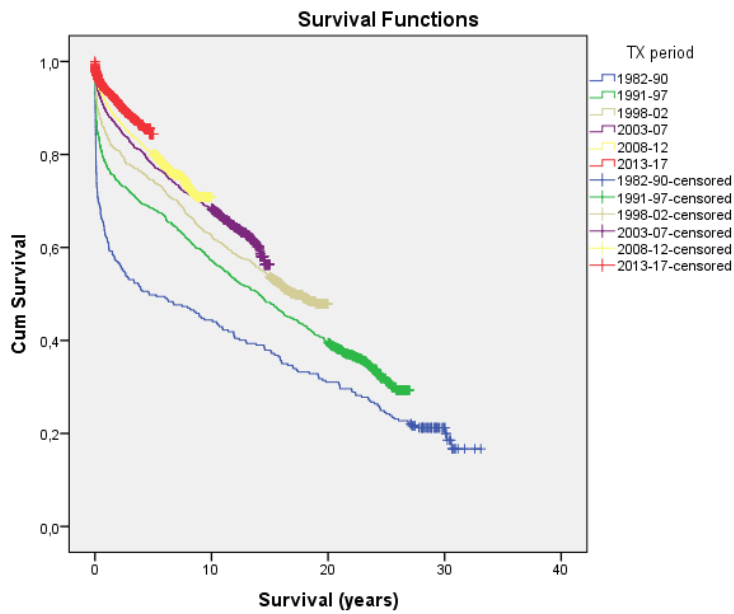


Figure 12. Kaplan-Meier patient survival curve for patients receiving a first liver allograft in the indicated time periods.

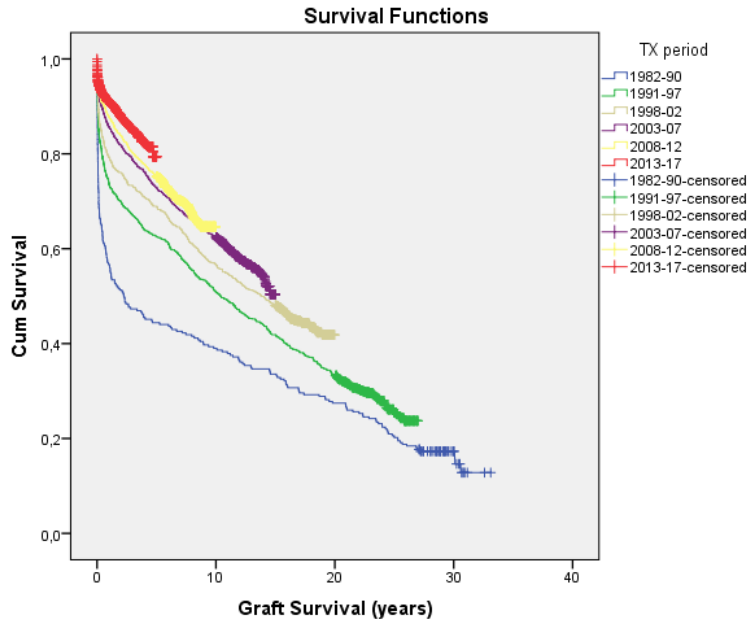


Figure 13. Kaplan-Meier graft survival curve for patients receiving a first liver allograft in the indicated time periods.

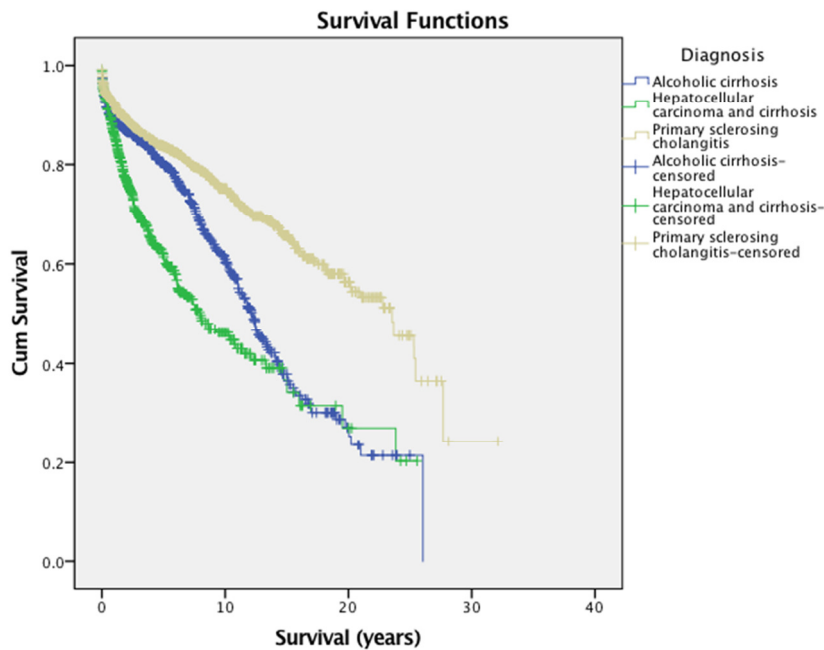


Figure 14. Kaplan-Meier patient survival curve for patients receiving a first liver allograft stratified for the three most common primary diagnoses.

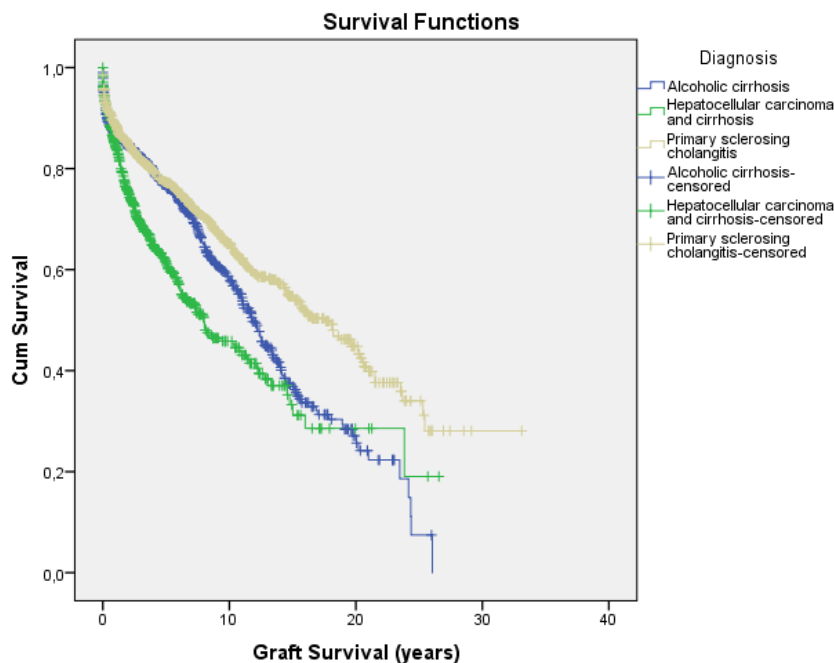


Figure 15. Kaplan-Meier graft survival curve for patients receiving a first liver allograft stratified for the three most common primary diagnoses.

	Median age	1-year survival (%)	5-year survival (%)
Primary sclerosing cholangitis	43,2	97 %	89 %
Hepatocellular carcinoma and cirrhosis	59,8	93 %	72 %
Alcoholic cirrhosis	57,4	93 %	85 %
Metabolic disease	51,5	94 %	89 %
Autoimmune cirrhosis	47,5	90 %	86 %
Cirrhosis - unknown	55,3	91 %	82 %
Extrahepatic biliary atresia	1,2	88 %	83 %
Polycystic disease	53,5	95 %	94 %
Primary biliary cirrhosis	57,0	95 %	87 %
Post hepatitis C cirrhosis	54,3	90 %	77 %
Listed as highly urgent	42,3	83 %	78 %

Table 7. Survival for the patients listed 2006-2017 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 2017. 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 and in Helsinki, Helena Isoniemi with help of Leena Toivonen is overseeing the maintenance of the registry. I am also grateful for the start-up of collaborating with Tartu where Virge Pall has been very supportive. 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. During 2017 we finished adjustments that would allow us to transfer data to ELTR and most centers have signed an agreement with ELTR to allow this. From NLTR this process is finished and regular data transfer can take place.

9. Acknowledgements - financial support

The NLTR received no financial support in 2017. 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 1990-2017:

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
5. Bjøro K, Höckerstedt K, Ericzon BG, Friman S, Hjortrup A, Keiding S, Schrumpf E, Duraj F, Olausson M, Mäkisalo H, Bergan A, Kirkegaard P. Liver transplantation in patients over 60 years of age. *Transpl Int* 2000; 13, 165-170 6. Bjøro K, Kirkegaard P, Ericzon BG, Friman S, Schrumpf E, Isoniemi H, Herlenius G, Olausson M, Rasmussen A, Foss A, Höckerstedt K. Is a 3-day limit for highly urgent liver transplantation for fulminant hepatic failure appropriate – or is the diagnosis in some cases incorrect? *Transpl Proceed* 2001;33:2511-3

7. Ericzon BG, Bjøro K, Höckerstedt K, Hansen B, Olausson M, Isoniemi H, Kirkegaard P, Broome U, Foss A, Friman S. Time to request ABO-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.
9. Olausson M, Mjornstedt L, Backman L, Lindner P, Olsson R, Krantz M, Karlsten KL, Stenqvist O, Henriksson BA, Friman S. Liver transplantation--from experiment to routine care. Experiences from the first 500 liver transplantations in Gothenburg. *Lakartidningen* 2001;98:4556-62
10. Brandsæter B, Höckerstedt K, Ericzon BG, Friman S, Kirkegaard P, Isoniemi H, 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. Brandsæter B, Friman S, Broome U, Isoniemi H, Olausson M, Backman L, Hansen B, Schrumpf E, Oksanen A, Ericzon BG, Höckerstedt K, Mäkisalo H, Kirkegaard P, Bjøro K. Outcome

following liver transplantation for primary sclerosing cholangitis in the Nordic countries. *Scand J Gastroenterol.* 2003;38:1176-83.

14. Brandsaeter B, Isoniemi H, Broome U, Olausson M, Backman L, Hansen B, Schrumpf E, Oksanen A, Ericzon BG, Höckerstedt K, Makisalo H, Kirkegaard P, Friman S, Bjoro K. Liver transplantation for primary sclerosing cholangitis; predictors and consequences of hepatobiliary malignancy. *J Hepatol.* 2004;40:815-822.

15. Bjøro K, Schrumpf E. Liver transplantation for primary sclerosing cholangitis. *J Hepatol.* 2004;40:570-7.

16. Brandsaeter B, Isoniemi H, Broomé U, Olauson M, Bäckmann L, Hansen B, Oksanen A, Ericzon BG, Höckerstedt K, Mäkisalo H, Kirkegaard P, Friman S, Bjøro K, Schrumpf E (Nordic Liver Transplantation Group). Chemopreventive effect of ursodeoxycholic acid in primary sclerosing cholangitis? Falk Symposium 141. Bile Acid Biology and its Therapeutic Implications. XVIII International Bile Acid Meeting 2005;242-249.

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.

18. Bjøro K, Brandsaeter B, Foss A, Schrumpf E. Liver transplantation in primary sclerosing cholangitis. *Semin Liver Dis.* 2006;26:69-79.

19. Melum E, Friman S, Bjøro K, Rasmussen A, Isoniemi H, Gjertsen H, Bäckman L, Oksanen A, Olausson M, Duraj FF, Ericzon BG. Hepatitis C impairs survival following liver transplantation irrespective of concomitant hepatocellular carcinoma. *J Hepatol.* 2007;47:777-83.

20. Friman S, Foss A, Isoniemi H, Olausson M, Höckerstedt K, Yamamoto S, Karlsen TH, Rizell M, Ericzon BG. Liver transplantation for cholangiocarcinoma: selection is essential for

acceptable results. *Scand J Gastroenterol.* 2011;46:370-5.

21. Jørgensen KK, Lindström L, Cvancarova M, Castedal M, Friman S, Schrumpf E, Foss A, Isoniemi H, Nordin A, Holte K, Rasmussen A, Bergquist A, Vatn MH, Boberg KM. Colorectal neoplasia in patients with primary sclerosing cholangitis undergoing liver transplantation: a Nordic multicenter study. *Scand J Gastroenterol.* 2012;47:1021-9.

22. Jørgensen KK, Lindström L, Cvancarova M, Karlsen TH, Castedal M, Friman S, Schrumpf E, Foss A, Isoniemi H, Nordin A, Holte K, Rasmussen A, Bergquist A, Vatn MH, Boberg KM. Immunosuppression after liver transplantation for primary sclerosing cholangitis influences activity of inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2013;11:517-23

23. Fosby B, Melum E, Bjørø K, Bennet W, Rasmussen A, Andersen IM, Castedal M, Olausson M, Wibeck C, Gotlieb M, Gjertsen H, Toivonen L, Foss S, Makisalo H, Nordin A, Sanengen T, Bergquist A, Larsson ME, Soderdahl G, Nowak G, Boberg KM, Isoniemi H, Keiding S, Foss A, Line PD, Friman S, Schrumpf E, Ericzon BG, Höckerstedt K, Karlsen TH. Liver transplantation in the Nordic countries - An intention to treat and post-transplant analysis from The Nordic Liver Transplant Registry 1982-2013. *Scand J Gastroenterol.* 2015;50:797-808.

24. Thorsen T, Aandahl EM, Bennet W, Olausson M, Ericzon BG, Nowak G, Duraj F, Isoniemi H, Rasmussen A, Karlsen TH, Foss A. Transplantation With Livers From Deceased Donors Older Than 75 Years. *Transplantation.* 2015;99:2534-42

25. Åberg F, Gissler M, Karlsen TH, Ericzon BG, Foss A, Rasmussen A, Bennet W, Olausson M, Line PD, Nordin A, Bergquist A, Boberg KM, Castedal M, Pedersen CR, Isoniemi H. Differences in long-term survival among liver transplant recipients and the general population: a population-based Nordic study. *Hepatology.* 2015;61:668-77

26. Malenicka S, Ericzon BG, Jørgensen MH, Isoniemi H, Karlsen TH, Krantz M, Naeser V, Olausson M, Rasmussen A, Rönnholm K, Sanengen T, Scholz T, Fischler B, Nemeth A. Impaired intention-to-treat survival after listing for liver transplantation in children with biliary atresia compared to other chronic liver diseases: 20 years' experience from the Nordic countries. *Pediatr Transplant*. 2017 Mar;21(2). doi: 10.1111/ptr.12851