

2018 Annual Report of the European Liver Transplant Registry (ELTR) - 50-year evolution of liver transplantation

René Adam, Vincent Karam, Valérie Cailliez, John O Grady, Darius Mirza, Daniel Cherqui, Jurgen Klempnauer, Mauro Salizzoni, Johann Pratschke, Neville Jamieson, et al.

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ANNUAL REPORT

2018 Annual Report of the European Liver Transplant Registry (ELTR) – 50-year evolution of liver transplantation

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SUMMARY

The purpose of this registry study was to provide an overview of trends and results of liver transplantation (LT) in Europe from 1968 to 2016. These data on LT were collected prospectively from 169 centers from 32 countries, in the European Liver Transplant Registry (ELTR) beginning in 1968. This overview provides epidemiological data, as well as information on evolution of techniques, and outcomes in LT in Europe over more than five decades; something that cannot be obtained from only a single center experience.

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The order of the co-authors from 2 to 40 was determined according to the decreasing number of liver transplants recorded in the ELTR.
The list with all the centers is available at the following link: http://www.eltr.org/spip.php?page=centers-tous

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26 University Hospital, Innsbruck, Austria
27 University of Edinburgh Royal Infirmary, Edinburgh, UK
28 Hospital Universitari De Bellvitge, Barcelona, Spain
29 Papa Giovanni 23 Hospital, Bergamo, Italy
30 University Medical Center Groningen, Groningen, The Netherlands
31 Inonu Universitesi, Malatya, Turkey
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Introduction

Background of the European Liver Transplant Registry

Created in 1986, the ELTR has collected the data of liver transplantation (LT) from 175 centers all over Europe since 1968. The registered data represents more than 95% of the overall European data compared with the published official figures [1].

Questionnaire

The ELTR questionnaire includes data on indications for LT, donors and recipients characteristics, technical aspects of LT (with reduced, split, domino, live and nonheart beating donors), initial and current regimen of immunosuppression, patient outcomes, and cause of death or graft failure. The ELTR has developed an online application (Electronic Data Capture – EDC) for collecting data. A Web-based module was developed to allow for real-time data capture. Software, questionnaires, validation routines, and statistics are located on a central server, which can be accessed by the participating centers with a standard internet browser [2].

To avoid an overlap in case of multiple diagnoses, the ELTR has two variables to report the diagnosis (Disease1 & Disease2) and an open field for specification in case a diagnosis is not available in the official pull-down menu, or in case there are more than two combined diagnoses. A standard procedure was stated accordingly for the data entry and their analysis in each condition.

Quality control of the data

The data-entry process is dynamically controlled. The data are subjected to routine checks for completeness, consistency, and range. Comprehensive logical intra- and inter-updates are performed. In addition, a control of the good adequacy between ELTR questionnaire and patient charts is performed by randomly conducted audit visits to the centers. The ELTR audit visits have been continuously conducted since 1998 with, initially 10 randomly selected centers per year up to the year 1999, and five centers per year since 2000. Two auditors perform the visit with the condition that both are not from the visited country. Ten percent of center's files, with a minimum of 20 and a maximum of 50, are analyzed to check data for completeness and consistency. The audit visits serve also to train staff members, and to introduce amendments in the procedure. It is also the opportunity to meet

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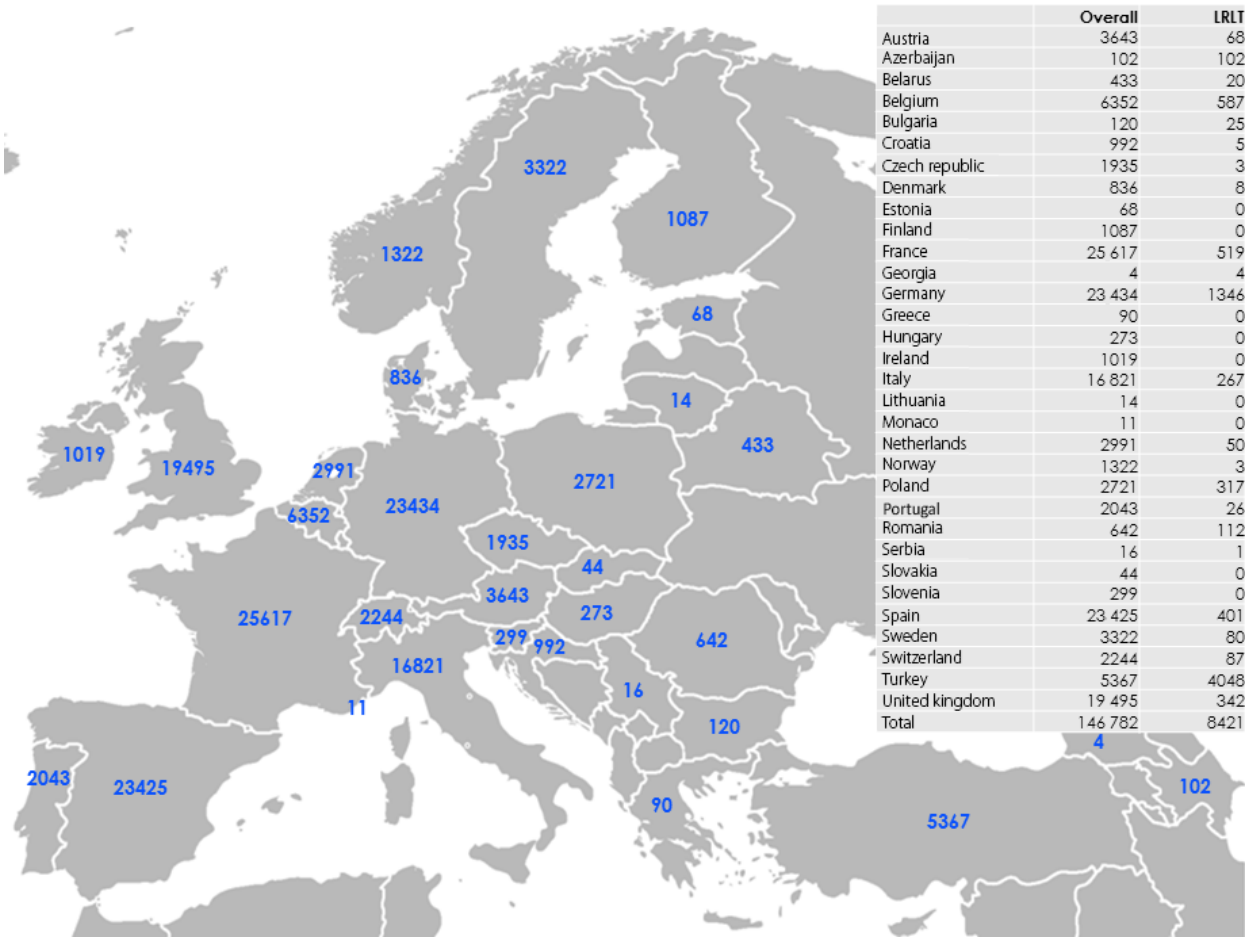
with the staff of centers, something that is valuable for creating a team spirit. The ELTR is considered as the pioneer of external audit visits of a scientific registry. The audit report is sent confidentially to the head of the center with all the discrepancies noted, and the recommendations necessary to improve the data entry included. The results of all center audits are presented during the ELTR biennial workshops, where all the contributing centers are invited. A recent analysis of the ELTR audit data (38 centers from 16 countries, 57 575 variables from 1458 patient files, from 2010 to 2016) showed that the overall rates of completeness and consistency were 94.5% and 97.3% respectively. Audit visits are an indicator of the quality of data, and represent one of the pillars of the ELTR. These results have indicated that ELTR data are reliable, and the scientific results of ELTR can be considered credible and representative of LT in Europe [3–6].

Partnership with organ sharing organizations (OSOs)

The ELTR has established agreements with the main national and international OSOs: United Kingdom Transplant Service Support Authority – UK NHS Blood and Transplant, Spanish Organizacion Nacional de Trasplantes – ONT, Scandinavian Scandiatransplant – SKT, Dutch Transplant Foundation – NTS, Eurotransplant Foundation – ET, French Agence de la Biomédecine – ABM to exchange data collected from European Centers and to cross check common data between OSO and ELTR.

Source of the data

There are two sources of ELTR data; 72% of data (63% of centers) are shared with the OSOs and 28% of data (37% of centers) are directly entered into the ELTR EDC platform. Some variables were added to the



	Overall	LRLT
Austria	3643	68
Azerbaijan	102	102
Belarus	433	20
Belgium	6352	587
Bulgaria	120	25
Croatia	992	5
Czech republic	1935	3
Denmark	836	8
Estonia	68	0
Finland	1087	0
France	25 617	519
Georgia	4	4
Germany	23 434	1346
Greece	90	0
Hungary	273	0
Ireland	1019	0
Italy	16 821	267
Lithuania	14	0
Monaco	11	0
Netherlands	2991	50
Norway	1322	3
Poland	2721	317
Portugal	2043	26
Romania	642	112
Serbia	16	1
Slovakia	44	0
Slovenia	299	0
Spain	23 425	401
Sweden	3322	80
Switzerland	2244	87
Turkey	5367	4048
United kingdom	19 495	342
Total	146 782	8421

Figure 1 Number of LTs performed in each country, overall and living related liver transplantation (LRLT)(May 1968–December 2016).

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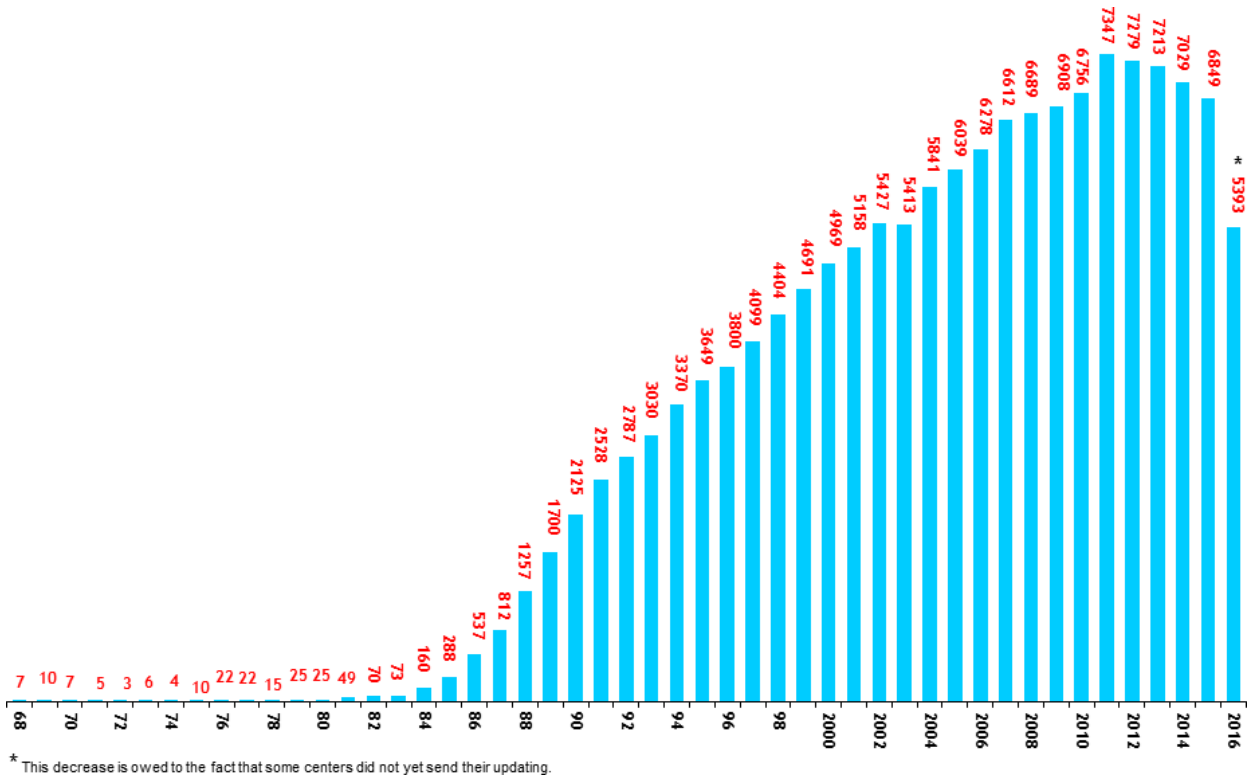


Figure 2 Evolution of 147 161 LTs performed in Europe since May 1968.

questionnaire, and some definitions have changed since the registry was created in 1986. To adapt the ELTR to these evolutions, an experts committee was appointed to oversee the standardization of the questionnaire. The European Liver and Intestine Transplant Association (ELITA) board and the OSOs share this concern and are also attentive to all the evolutions.

Previous ELTR achievements

The ELTR regularly carries out thematic studies related to the different fields of LT. These studies minimize the potential biases, by assessing interactions between confounding factors and identification of independent predictors among all the ELTR variables that can have an impact on the outcome. A sample of these studies is cited in the references of the manuscript. With reports concerning LT for specific hepatic diseases [7–24], analysis of the impact of the type of preservation solution [25], and of the immunosuppressive regimen on the patient outcome [26], ELTR has helped develop risk models for mortality following liver-transplantation [27,28]. Owing to the large cohort of patients, the exhaustiveness, and quality of the data, and the long follow-up provided by the ELTR, the results are really representative of LT in Europe.

The objective of this paper is to report these results and their evolution in adults as well as in pediatric recipients.

Patients and methods

The whole data since 1968 was considered initially to show the evolution of results of LT in Europe since its initial development. The rest of analysis was then undertaken considering two different periods: (i) January 1988 to December 2016 (147 161 LT – 127 851 patients) [January 1988 was chosen corresponding to the introduction and widespread use of cyclosporine-based immunosuppression, and standardization of the surgical procedure], (ii) the last 15-year period data from January 2002 to December 2016 (99 562 LT – 91 183 patients) to give a more recent evaluation of LT results in Europe.

Data were generally analyzed as a whole (except for some variables), without making a distinction between adult and pediatric population, the latter representing 10% of LT in Europe.

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Table 1. Primary indication of LT in Europe and the corresponding graft and patient survival rate.

	From 1988 to 2016										Last 15 years									
Indication of LT	*N* patients	% of the disease	% of the Total	Survival rate	*N*	1 year, %	5 years, %	10 years, %	15 years, %	20 years, %	*N* patients	% of the disease	% of the Total	Survival rate	*N*	1 year, %	5 years, %	10 years, %	15 years, %	
Acute hepatic failure	9485		7	Graft	9268	66	58	52	45	37	6240		7	Graft	6080	70	62	55	46	
				Patient	9247	72	65	59	54	46				Patient	6071	76	69	62	55	
Fulminant or Subfulminant hepatitis	7485		6	Graft	7291	66	59	53	46	38	4606		5	Graft	4466	71	64	57	50	
				Patient	7272	72	66	60	54	47				Patient	4458	76	70	64	57	
Virus A	163	2	0.1	Graft	160	61	57	52	43	32	111	2	0.1	Graft	109	65	61	61		
				Patient	159	63	60	56	48	43				Patient	108	67	62	62		
Virus B	917	12	1	Graft	909	69	62	57	50	40	578	13	1	Graft	571	74	67	64	52	
				Patient	905	75	68	63	57	47				Patient	570	78	73	69	61	
Virus C	127	2	0.1	Graft	125	65	53	39	32	25	80	2	0.1	Graft	78	68	50	35		
				Patient	125	72	58	42	39	27				Patient	78	74	54	40		
Virus D	14	0.2	0.01	Graft	14	76	67	46	46	46	4	0.1	0.004	Graft	4	100	100	67	67	
				Patient	14	76	67	56	56	56				Patient	4	100	100	100	100	
Other known	797	11	1	Graft	776	68	61	56	49	40	565	12	1	Graft	547	71	64	57		
				Patient	776	73	68	64	55	48				Patient	547	76	71	64		
Other unknown	3647	49	3	Graft	3585	65	58	53	46	39	1966	43	2	Graft	1922	71	65	59	50	
				Patient	3576	71	65	60	55	48				Patient	1918	77	71	65	57	
Paracetamol	743	10	1	Graft	671	69	59	50	45	32	531	12	1	Graft	477	74	64	53	43	
				Patient	668	74	65	58	54	43				Patient	476	78	70	63	59	
Other drug related: specify	715	10	1	Graft	692	68	62	49	44	35	472	10	1	Graft	461	72	66	56	56	
				Patient	691	72	67	56	50	42				Patient	461	77	71	61	61	
Toxic (nondrug)	362	5	0.3	Graft	359	63	58	51	44	29	299	6	0.3	Graft	297	63	58	48	48	
				Patient	358	68	64	58	51	45				Patient	296	68	63	54	54	
Traumatic acute hepatic failure	430		0.3	Graft	430	48	39	35	31	31	346		0.4	Graft	346	52	41	36		
				Patient	429	57	48	44	43	43				Patient	346	61	51	44		
Postoperative	173	40	0.1	Graft	173	30	20	17			138	40	0.2	Graft	138	33	21	17		
				Patient	173	45	34	29	24	24				Patient	138	48	38	30		
Post-traumatic	257	60	0.2	Graft	257	61	52	48	45	45	208	60	0.2	Graft	208	65	55	49		
				Patient	256	65	57	54	54	54				Patient	208	69	60	54		
Subacute hepatic failure	1570		1								1288		1							
Virus A	10	1	0.01	Graft	10	67	50				8	1	0.01	Graft	8	71	48			
				Patient	10	67	50							Patient	8	71	48			
Virus B	130	8	0.1	Graft	127	80	65	54	20		113	9	0.1	Graft	111	80	68	63		
				Patient	127	85	67	61	49					Patient	111	85	72	66	66	
Virus C	184	12	0.1	Graft	184	75	56	32	18		161	13	0.2	Graft	161	75	55	33		
				Patient	183	78	60	36	28					Patient	160	79	58	34		
Virus D	6	0.4	0.005	Graft	6	67	67	67			4	0.3	0.004	Graft	4	75	75	75		
				Patient	6	83	83	56						Patient	4	75	75	75		
Other known	62	4	0.05	Graft	61	76	66	66	66	66	54	4	0.1	Graft	53	80	68	68		
				Patient	61	79	71	64	64	64				Patient	53	84	74	63		
Other unknown	278	18	0.2	Graft	267	77	67	62	55	45	207	16	0.2	Graft	198	80	71	67	58	
				Patient	267	81	75	71	65	53				Patient	198	84	79	76	64	
Paracetamol	5	0.3	0.004	Graft	5	67	67				4	0.3	0.004	Graft	4	100	100			
				Patient	5	67	67							Patient	4	100	100			
Other drug related: specify	60	4	0.05	Graft	56	62	55	49	41	41	51	4	0.1	Graft	47	66	57	53		
				Patient	56	70	65	56	49	49				Patient	47	70	65	55		
Toxic (non drug)	24	2	0.02	Graft	23	78	68	54	27		17	1	0.02	Graft	16	87	80	80		
				Patient	23	78	73	58	58					Patient	16	87	87	87		
Other acute hepatic failure: specify	811	52	1	Graft	808	65	54	46	40	29	669	52	1	Graft	666	67	53	46	25	
				Patient	808	72	63	55	51	45				Patient	666	74	62	54	48	

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Table 1. Continued.

Indication of LT	From 1988 to 2016										Last 15 years									
	N patients	% of the disease	% of the Total	Survival rate	*N*	1 year, %	5 years, %	10 years, %	15 years, %	20 years, %	*N* patients	% of the disease	% of the Total	Survival rate	*N*	1 year, %	5 years, %	10 years, %	15 years, %	
Fulminant or subfulminant or subacute hepatitis	11 625		9								7638		8							
Viral	1551	13	1	Graft	1535	70	60	53	45	36	1054	14	1	Graft	1046	73	63	57	46	
				Patient	1529	75	66	58	52	43				Patient	1043	78	68	61	55	
Virus B	1047	9	1	Graft	1036	71	62	57	49	40	691	9	1	Graft	682	75	67	64	51	
				Patient	1032	76	69	63	57	47				Patient	681	80	73	69	61	
Drug-related	1523	13	1	Graft	1424	68	60	50	44	34	1058	14	1	Graft	989	73	65	55	50	
				Patient	1420	73	66	57	52	43				Patient	988	77	70	62	60	
Paracetamol	748	6	1	Graft	676	69	59	50	45	32	535	7	1	Graft	481	75	64	53	43	
				Patient	673	74	65	58	54	43				Patient	480	78	70	63	59	
Other drugs	775	7	1	Graft	748	68	61	49	44	35	523	7	1	Graft	508	72	65	56	56	
				Patient	747	72	66	56	50	42				Patient	508	76	70	61	61	
Toxic (nondrug)	386	3	0.3	Graft	382	64	59	51	44	29	316	4	0.3	Graft	313	64	59	49	46	
				Patient	381	69	65	58	51	45				Patient	312	69	65	56	56	
Unknown or others	5595	48	4	Graft	5497	66	59	53	47	39	3461	45	4	Graft	3386	71	63	57	46	
				Patient	5488	72	66	61	55	48				Patient	3382	77	70	64	55	
Cholestatic disease	13 241		10	Graft	12 917	82	73	62	50	38	8439		9	Graft	8242	84	74	63	52	
				Patient	12 883	87	79	71	59	46				Patient	8221	90	81	73	62	
Secondary biliary cirrhosis	976	7	1	Graft	955	72	62	54	47	39	693	8	1	Graft	679	73	62	54	49	
				Patient	955	79	69	62	56	48				Patient	679	80	69	63	58	
Primary biliary cholangitis	5865	44	5	Graft	5698	83	76	66	54	41	3050	36	3	Graft	2971	86	78	68	59	
				Patient	5688	87	80	71	58	45				Patient	2966	90	83	74	64	
Primary sclerosing cholangitis	5786	44	5	Graft	5682	83	71	58	45	31	4248	50	5	Graft	4172	85	73	59	46	
				Patient	5663	89	80	71	60	46				Patient	4160	91	82	74	60	
Other cholestatic disease: specify	614	5	0.5	Graft	582	80	74	68	58	50	448	5	0.5	Graft	420	79	71	66	62	
				Patient	577	86	82	78	69	64				Patient	416	86	80	77	71	
Congenital biliary disease	6397		5	Graft	6248	82	77	73	68	63	4274		5	Graft	4180	85	81	77	68	
				Patient	6234	88	85	83	80	76				Patient	4174	91	88	87	85	
Caroli disease	258	4	0.2	Graft	257	81	74	66	57	52	207	5	0.2	Graft	206	82	74	62		
				Patient	257	89	84	80	70	66				Patient	206	90	86	78	78	
Extrahepatic biliary atresia	5232	82	4	Graft	5107	82	77	74	70	64	3403	80	4	Graft	3326	86	82	78	74	
				Patient	5095	89	85	83	81	78				Patient	3322	92	89	88	86	
Congenital biliary fibrosis	194	3	0.2	Graft	192	80	77	67	63	61	138	3	0.2	Graft	136	83	78	66	66	
				Patient	192	88	85	75	71	69				Patient	136	90	88	75	75	
Choledocal cyst	41	1	0.03	Graft	41	87	80	54	36		21	0.5	0.02	Graft	21	79	63	42		
				Patient	41	87	87	76	76					Patient	21	79	79	59		
Alagille syndrome	338	5	0.3	Graft	335	82	77	74	69	69	261	6	0.3	Graft	258	85	81	79	75	
				Patient	335	88	84	80	77	72				Patient	258	90	87	85	80	
Other congenital biliary disease: specify	334	5	0.3	Graft	316	83	75	68	54	44	244	6	0.3	Graft	233	83	75	70	21	
				Patient	314	88	81	78	68	62				Patient	231	89	83	82	75	
Cirrhosis	64 166		50	Graft	63 140	80	67	55	43	32	45 566		50	Graft	44 806	82	68	55	42	
				Patient	63 062	84	71	59	47	36				Patient	44 758	85	72	59	46	
Alcoholic cirrhosis	24 380	38	19	Graft	24 030	82	70	55	41	29	18 135	40	20	Graft	17 849	83	71	55	40	
				Patient	24 005	85	74	58	43	31				Patient	17 830	86	75	59	43	
Autoimmune Cirrhosis	2929	5	2	Graft	2850	81	71	60	48	38	2027	4	2	Graft	1978	83	74	63	45	
				Patient	2843	86	77	68	57	48				Patient	1974	88	80	72	57	
Virus B related cirrhosis	5822	9	5	Graft	5746	80	70	64	56	48	3826	8	4	Graft	3774	82	72	66	57	
				Patient	5739	84	74	68	61	52				Patient	3770	86	76	70	62	

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Table 1. Continued.

Indication of LT	From 1988 to 2016										Last 15 years									
	N patients	% of the disease	% of the Total	Survival rate	*N*	1 year, %	5 years, %	10 years, %	15 years, %	20 years, %	*N* patients	% of the disease	% of the Total	Survival rate	*N*	1 year, %	5 years, %	10 years, %	15 years, %	
Virus C related cirrhosis	15 187	24	12	Graft	15 062	77	60	47	37	26	10 495	23	12	Graft	10 396	78	59	46	36	
				Patient	15 051	80	64	52	41	30				Patient	10 387	81	64	51	40	
Virus BD related cirrhosis	1939	3	2	Graft	1899	89	84	79	74	67	1431	3	2	Graft	1403	89	84	79	75	
				Patient	1895	92	88	84	81	73				Patient	1401	93	89	83	78	
Virus BC related cirrhosis	829	1	1	Graft	819	78	64	54	42	31	559	1	1	Graft	552	80	66	54	34	
				Patient	818	82	70	60	47	33				Patient	551	83	71	60	39	
Virus BCD related cirrhosis	174	0.3	0.1	Graft	170	88	78	62	47	47	134	0.3	0.1	Graft	130	88	78	67		
				Patient	170	90	80	67	45	45				Patient	130	89	81	69		
Virus related cirrhosis-Other viruses: specify	1994	3	2	Graft	1780	83	64	49	35	24	1353	3	1	Graft	1208	86	66	52	39	
				Patient	1766	85	68	54	40	27				Patient	1203	89	71	57	44	
Combined virus C and alcoholic cirrhosis	1996	3	2	Graft	1980	82	65	50	36	24	1531	3	2	Graft	1515	83	66	51	38	
				Patient	1980	85	69	55	41	27				Patient	1516	86	70	56	44	
Combined virus B and alcoholic cirrhosis	489	1	0.4	Graft	485	87	74	61	53	53	382	1	0.4	Graft	379	88	77	68		
				Patient	484	90	78	64	55	55				Patient	379	91	80	70		
Posthe patitic cirrhosis-Drug related	77	0.1	0.1	Graft	77	78	63	46	33		44	0.1	0.05	Graft	44	84	65			
				Patient	77	79	67	52	34					Patient	44	84	70	34		
Other cirrhosis: specify	2732	4	2	Graft	2728	77	64	55	47	38	1841	4	2	Graft	1837	78	66	55	45	
				Patient	2727	81	69	59	51	42				Patient	1836	83	71	59	48	
Cryptogenic (unknown) cirrhosis	5618	9	4	Graft	5514	78	67	56	46	34	3808	8	4	Graft	3741	80	69	57	45	
				Patient	5507	81	72	61	50	37				Patient	3737	83	73	61	47	
Primary liver tumors	21 135		17	Graft	20 976	81	60	47	36	28	17 329		19	Graft	17 206	83	64	49	37	
				Patient	20 971	84	64	50	39	31				Patient	17 202	87	67	53	40	
Hepatocellular carcinoma and cirrhosis	18 349	87	14	Graft	18 225	82	62	48	36	28	15 617	90	17	Graft	15 510	84	65	49	38	
				Patient	18 220	86	66	51	39	31				Patient	15 506	87	68	53	40	
Hepatocellular carcinoma and noncirrhotic liver	734	3	1	Graft	726	72	49	34	24	18	425	2	0.5	Graft	423	81	61	44		
				Patient	726	77	52	37	27	20				Patient	423	87	66	48	24	
Hepatocellular carcinoma – Fibrolamellar	51	0.2	0.04	Graft	51	76	38	33	27	27	26	0.2	0.03	Graft	26	85	45			
				Patient	51	80	41	36	36	36				Patient	26	88	47			
Biliary tract carcinoma (Klatskin)	395	2	0.3	Graft	394	65	34	26	16	13	245	1	0.3	Graft	244	67	35	25		
				Patient	394	72	41	35	24	21				Patient	244	76	47	41		
Hepatic cholangiocellular carcinoma	530	3	0.4	Graft	526	66	32	23	16	14	306	2	0.3	Graft	306	73	40	31	17	
				Patient	526	69	33	25	19	15				Patient	306	77	42	32	22	
Hepatoblastoma	377	2	0.3	Graft	372	83	75	71	70	61	330	2	0.4	Graft	325	84	77	73	73	
				Patient	372	87	80	77	75	66				Patient	325	88	83	79	79	
Epithelioid hemangioendothelioma	216	1	0.2	Graft	213	85	72	67	61	58	161	1	0.2	Graft	158	85	73	65	60	
				Patient	213	90	77	71	67	60				Patient	158	91	79	71	65	
Angiosarcoma	17	0.1	0.01	Graft	17	35					3	0.02	0. 003	Graft	3	67				
				Patient	17	38								Patient	3	67				
Other liver malignancies: specify	466	2	0.4	Graft	452	70	46	40	33	28	216	1	0.2	Graft	211	82	62	57		
				Patient	452	73	49	44	36	31				Patient	211	85	65	62		
Secondary liver tumors	639		0.5	Graft	636	75	48	32	24	19	395		0.4	Graft	393	79	57	44	33	
				Patient	636	80	52	34	26	21				Patient	393	85	61	46	36	
Carcinoid	341	53	0.3	Graft	339	78	52	34	24	19	185	47	0.2	Graft	183	83	64	51	38	
				Patient	339	82	55	36	27	22				Patient	183	87	67	54	41	

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Table 1. Continued.

Indication of LT	From 1988 to 2016										Last 15 years									
	N patients	% of the disease	% of the Total	Survival rate	*N*	1 year, %	5 years, %	10 years, %	15 years, %	20 years, %	*N* patients	% of the disease	% of the Total	Survival rate	*N*	1 year, %	5 years, %	10 years, %	15 years, %	
Other neuroendocrine	188	29	0.1	Graft	188	74	51	40	34		140	35	0.2	Graft	140	76	56	44	36	
				Patient	188	80	56	43	35					Patient	140	83	61	45	37	
Colorectal	73	11	0.1	Graft	72	73	24	3			53	13	0.1	Graft	53	81	24			
				Patient	72	80	26	3						Patient	53	85	29			
GI noncolorectal	18	3	0.01	Graft	18	60	35	20	10		8	2	0.01	Graft	8	45	23	23	23	
				Patient	18	60	35	20	10					Patient	8	45	23	23	23	
Nongastrointestinal	19	3	0.01	Graft	19	61	41	20			9	2	0.01	Graft	9	76	57			
				Patient	19	72	50	27						Patient	9	100	80			
Metabolic disease	7414		6	Graft	7188	82	73	64	55	48	5336		6	Graft	5166	83	74	63	52	
				Patient	7163	87	79	71	63	56				Patient	5147	88	80	71	60	
Wilson disease	1241	17	1	Graft	1200	83	78	71	64	56	904	17	1	Graft	879	85	79	72	65	
				Patient	1191	89	86	81	76	69				Patient	875	92	87	82	77	
Hemochromatosis	622	8	0.5	Graft	610	74	63	48	36	28	399	7	0.4	Graft	390	77	65	47	40	
				Patient	609	77	66	51	38	29				Patient	389	80	69	50	41	
Alpha-1 – Antitrypsin deficiency	717	10	1	Graft	678	83	75	66	58	44	478	9	1	Graft	457	84	76	68	54	
				Patient	678	87	81	72	65	56				Patient	457	88	81	73	61	
Glycogen storage disease	145	2	0.1	Graft	142	87	84	77	68	68	118	2	0.1	Graft	115	88	83	69		
				Patient	142	94	92	86	76	76				Patient	115	95	92	81		
Homozygous Hypercholesterolemia	36	0.5	0.03	Graft	36	86	81	65	65	65	29	1	0.03	Graft	29	85	80			
				Patient	36	86	81	81	81	81				Patient	29	85	80			
Tyrosinemia	122	2	0.1	Graft	119	85	75	73	71	65	65	1	0.1	Graft	62	87	84	84		
				Patient	118	91	86	84	84	84				Patient	62	90	87	87		
Familial amyloidotic polyneuropathy	1261	17	1	Graft	1241	82	73	62	50	38	866	16	1	Graft	847	83	73	62	50	
				Patient	1231	88	79	68	56	46				Patient	837	90	81	69		
Primary hyperoxaluria	332	4	0.3	Graft	326	79	72	62	53	50	264	5	0.3	Graft	258	78	73	61	33	
				Patient	326	84	77	68	58	58				Patient	258	84	79	67	25	
Protoporphyria	19	0.3	0.01	Graft	19	77	77	70	61	51	8	0.1	0.01	Graft	8	69	69			
				Patient	19	77	77	70	61	51				Patient	8	69	69			
Other porphyria	17	0.2	0.01	Graft	17	81	65	65			13	0.2	0.01	Graft	13	83	83			
				Patient	17	87	65	65						Patient	13	91	82			
Nonalcoholic steatohepatitis (NASH)	749	10	1	Graft	706	83	72	51			748	14	1	Graft	705	83	72	52		
				Patient	705	86	75	54						Patient	704	86	75	55		
Crigler-Najjar	93	1	0.1	Graft	88	86	74	72	72	72	65	1	0.1	Graft	60	84	70	66		
				Patient	88	94	89	89	89	89				Patient	60	95	91	91		
Cystic fibrosis	277	4	0.2	Graft	272	83	68	63	57	46	233	4	0.3	Graft	228	86	73	68		
				Patient	271	85	74	64	57	45				Patient	227	88	76	70		
Byler disease	251	3	0.2	Graft	250	85	81	78	71	71	137	3	0.2	Graft	136	88	82	74	59	
				Patient	250	94	92	89	85	85				Patient	136	94	92	90	79	
Other metabolic disease	1532	21	1	Graft	1484	81	71	63	55	49	1009	19	1	Graft	979	83	72	63	54	
				Patient	1482	86	77	71	63	57				Patient	977	88	79	72	65	
Budd Chiari	1069		1	Graft	1052	73	65	57	49	39	715		1	Graft	704	77	67	58	49	
				Patient	1051	79	72	65	57	49				Patient	704	82	74	65	57	
													0							
Benign liver tumors or Polycystic disease	1824		1	Graft	1804	85	80	70	60	52	1516		2	Graft	1499	87	81	71	60	
				Patient	1804	88	84	75	65	56				Patient	1499	90	86	76	64	
Hepatic adenoid	38	2	0.03	Graft	38	65	47	40	40	40	30	2	0.03	Graft	30	70	44	44		
				Patient	38	71	55	55	55	55				Patient	30	73	52	52		
Adenomatosis	51	3	0.04	Graft	49	81	81	81	81		45	3	0.05	Graft	43	81	81	81		
				Patient	49	87	87	87	87					Patient	43	88	88	88		
Hemangioma	71	4	0.1	Graft	71	75	69	64	64	64	45	3	0.05	Graft	45	73	64	64	64	
				Patient	71	80	77	71	71	71				Patient	45	75	69	69	69	

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Table 1. Continued.

Indication of LT	From 1988 to 2016										Last 15 years									
	N patients	% of the disease	% of the Total	Survival rate	*N*	1 year, %	5 years, %	10 years, %	15 years, %	20 years, %	*N* patients	% of the disease	% of the Total	Survival rate	*N*	1 year, %	5 years, %	10 years, %	15 years, %
Focal nodular hyperplasia	12	1	0.01	Graft	12	75	64	21			10	1	0.01	Graft	10	80	80	27	
				Patient	12	92	92	32						Patient	10	90	90	45	
Polycystic disease	1493	82	1	Graft	1478	87	82	73	62	52	1293	85	1	Graft	1280	88	83	73	61
				Patient	1478	90	86	78	67	54				Patient	1280	91	87	79	65
Nodular regenerative hyperplasia	25	1	0.02	Graft	25	88	71	71	36	36	17	1	0.02	Graft	17	100	83	83	
				Patient	25	88	71	71	36	36				Patient	17	100	83	83	
Other benign tumors: specify	134	7	0.1	Graft	131	79	71	60	49	44	76	5	0.1	Graft	74	82	73	56	56
				Patient	131	83	76	66	54	49				Patient	74	86	79	62	62
Parasitic disease	101		0.1	Graft	101	77	69	58	40	20	71		0.1	Graft	71	81	70	70	
				Patient	101	80	72	61	45	27				Patient	71	84	73	73	
Schistosomia (Bilharzia)	2	2	0.002	Graft	2	50	50	50	50		1	1	0.001	Graft					
				Patient	2	50	50	50	50					Patient					
Alveolar echinococcosis	58	57	0.05	Graft	58	88	80	66	66		49	69	0.1	Graft	49	90	78	78	
				Patient	58	90	81	67	67					Patient	49	92	80	80	
Cystic hydatidosis	11	11	0.01	Graft	11	72	57	57	29		8	11	0.01	Graft	8	74	49		
				Patient	11	71	57	57	28					Patient	8	74	49		
Other parasitic disease: specify	30	30	0.02	Graft	30	60	56	44	22	22	13	18	0.01	Graft	13	60	60	60	
				Patient	30	68	64	52	33	33				Patient	13	69	69	69	
Other liver disease	2380		2	Graft	2325	73	64	56	50	42	1302		1	Graft	1264	75	67	59	43
				Patient	2318	77	69	61	55	47				Patient	1263	80	72	64	49
TPN-induced cholestasis	11	0.5	0.01	Graft	11	71	54				10	1	0.01	Graft	10	68	46		
				Patient	11	71	54							Patient	10	68	46		
Hepatopulmonary syndrome	19	1	0.01	Graft	18	78	78				19	1	0.02	Graft	18	78	78		
				Patient	18	78	78							Patient	18	78	78		
Other liver diseases. nonspecified	2350	99	2	Graft	2296	73	64	56	50	42	1273	98	1	Graft	1233	75	67	59	43
				Patient	2289	77	69	61	55	47				Patient	1232	80	72	64	49
Total	127 851		100								91 183		100						

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Kaplan–Meier analysis was used to estimate graft and patient survival stratified by conditions group; statistical analyzes were performed using the log-rank test ($P < 0.05$ as significant) with SAS® Version 9.1.3 Entreprise Guide version 5.1 (Copyright© 2012 by SAS Institute Inc., Cary, NC, USA). The dynamics of data control was continued during the statistical analyzes. Calculation of survival rates was determined by the actuarial method.

Results

From May 1968 to December 2016, the ELTR has collected data concerning 146 782 LTs in 132 466 patients, from 169 Centers, and 32 countries (Fig. 1). These data give a comprehensive overview of the status and evolution of LT in Europe. Both the number of transplant centers and the annual number of LT's performed in Europe have gradually increased since the ELTR was created (Fig. 2). However, after an exponential increase from the eighties, a plateau seems to have been reached in recent years with about 7300 LTs performed all over Europe annually.

Main indications of LT in Europe

The main indications for LT in Europe with the corresponding graft and patient survival rates at 1, 5, 10, and 15 years in the whole ELTR population and in the last 15 years cohort are listed in Table 1. Twenty-year survival is provided for the whole ELTR population. Cirrhosis was the most frequent indication (50%), mainly related to either viral infection (22% with 12% of hepatitis C virus (HCV) infection and 5% of hepatitis B virus (HBV) infection), or to alcohol abuse (19%). Combined viral and alcoholic (ALD) cirrhosis represented 2.4% of indications, with 2% of HCV-ALD. Cirrhosis is followed by three major indications: primary liver tumors (17%, predominantly hepatocellular carcinoma – HCC, 15%), cholestatic liver diseases (10%), and acute hepatic failure (9.1%, 2% of which are virus-related, 2.4% drug related, 0.3% toxic nondrug related and 4.4% of unknown cause). The most common etiologies of the underlying cirrhosis in HCC patients were HCV (43%), ethanol abuse (27%), and HBV (16%). Cholestatic diseases included primary biliary cirrhosis (5%) and primary sclerosing cholangitis (5%). Biliary atresia (4%)

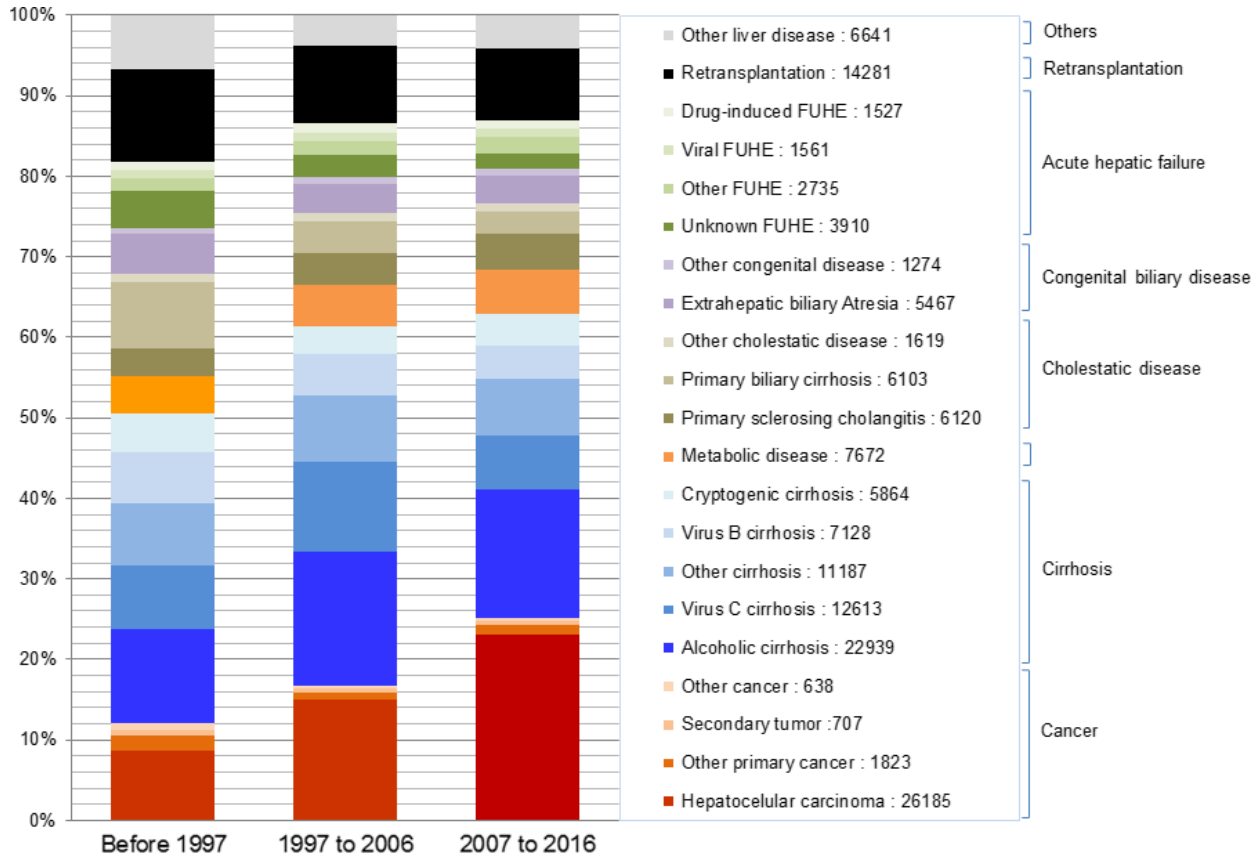


Figure 3 Evolution of indication according to three eras.

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represented the major congenital biliary disease. Metabolic diseases represented 6% of all the indications with three major indications being familial amyloidotic polyneuropathy, Wilson disease, and alpha-1-antitrypsin deficiency (1% each). Budd-Chiari and benign liver tumors (mainly polycystic disease) represented only 1% of the indications for LT. Secondary liver tumors (mainly neuroendocrine) represented 0.5% of LT's.

Indications for Pediatric liver transplants

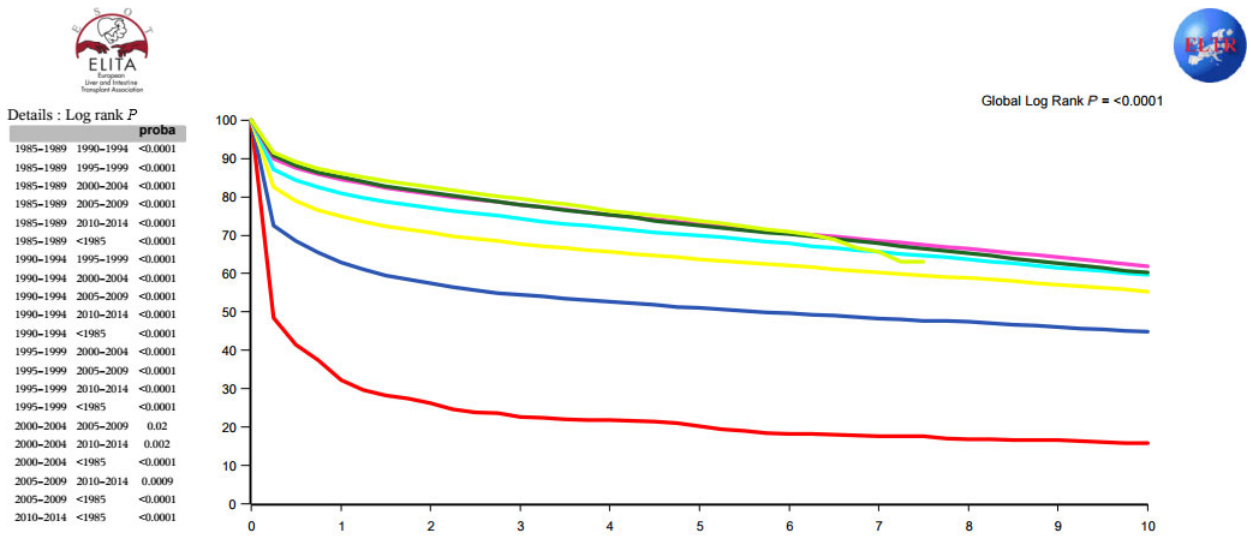
The proportions of the main indications for LT are differently distributed according to the age of recipients. While biliary atresia and metabolic diseases were the major indications in pediatric patients (≤18 years), cirrhosis with end stage liver disease, and cancer were the major indications in adults. An exponential increase in the proportion of cancer cases was noted with recipient age. Acute liver failure (ALF) mostly of unknown cause was frequent in young patients, with the highest incidence at 18–24 years.

Evolution of indications

The percentage of main indications has significantly changed with time (Fig. 3). Whereas cancers represented 12% of indications before 1997, their incidence has doubled in the last decade to represent currently more than 24%. Metabolic diseases and primary sclerosing cholangitis have slightly increased during the last decade. Conversely, while comparing the last decade with the previous one, we found that the proportion of cirrhosis alone, ALF and primary biliary cholangitis decreased. The decrease in cirrhosis is mainly because of the decrease in HCV cirrhosis, and the reduction in ALF cases is mainly because of the decline of ALF of unknown origin.

Survival according to the indication for LT

When all indications were considered, during the entire study period, patient survival rates were 83% at 1 year, 71% at 5 years, 61% at 10 years, 51% at 15 years, and



		proba
1985–1989	1990–1994	<0.0001
1985–1989	1995–1999	<0.0001
1985–1989	2000–2004	<0.0001
1985–1989	2005–2009	<0.0001
1985–1989	2010–2014	<0.0001
1985–1989	<1985	<0.0001
1990–1994	1995–1999	<0.0001
1990–1994	2000–2004	<0.0001
1990–1994	2005–2009	<0.0001
1990–1994	2010–2014	<0.0001
1990–1994	<1985	<0.0001
1995–1999	2000–2004	<0.0001
1995–1999	2005–2009	<0.0001
1995–1999	2010–2014	<0.0001
1995–1999	<1985	<0.0001
2000–2004	2005–2009	0.02
2000–2004	2010–2014	0.002
2000–2004	<1985	<0.0001
2005–2009	2010–2014	0.0009
2005–2009	<1985	<0.0001
2010–2014	<1985	<0.0001

Survival %

class of LT1 date	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
1985–1989	63%	57%	54%	53%	51%	50%	48%	47%	46%	45%
1990–1994	75%	71%	68%	66%	64%	62%	60%	59%	57%	55%
1995–1999	81%	77%	74%	72%	70%	68%	66%	64%	62%	60%
2000–2004	85%	81%	78%	75%	73%	71%	69%	66%	64%	62%
2005–2009	85%	81%	78%	75%	73%	70%	68%	65%	63%	60%
2010–2014	86%	83%	79%	76%	74%	71%	66%			
<1985	32%	26%	23%	22%	20%	18%	18%	17%	17%	16%

Number of exposed patients

	Total	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
1985–1989	3967	2464	2250	2132	2056	1990	1929	1861	1817	1749	1687
1990–1994	11 914	8806	8272	7901	7603	7332	7092	6822	6546	6241	5885
1995–1999	18 156	14 384	13 591	12 955	12 327	11 722	11 021	10 342	9743	9121	8620
2000–2004	23 773	18 963	17 420	16 272	15 294	14 421	13 645	12 832	12 016	11 215	10 292
2005–2009	28 813	22 636	20 468	18 755	17 480	15 977	14 319	11 412	7851	4776	2592
2010–2014	32 030	23 232	17 687	11 871	7277	3891	1189	98	0	0	0
<1985	472	152	124	107	103	95	86	83	78	77	74

Figure 4 Patient survival versus period of liver transplantation, n = 119 125 (1968–2016).

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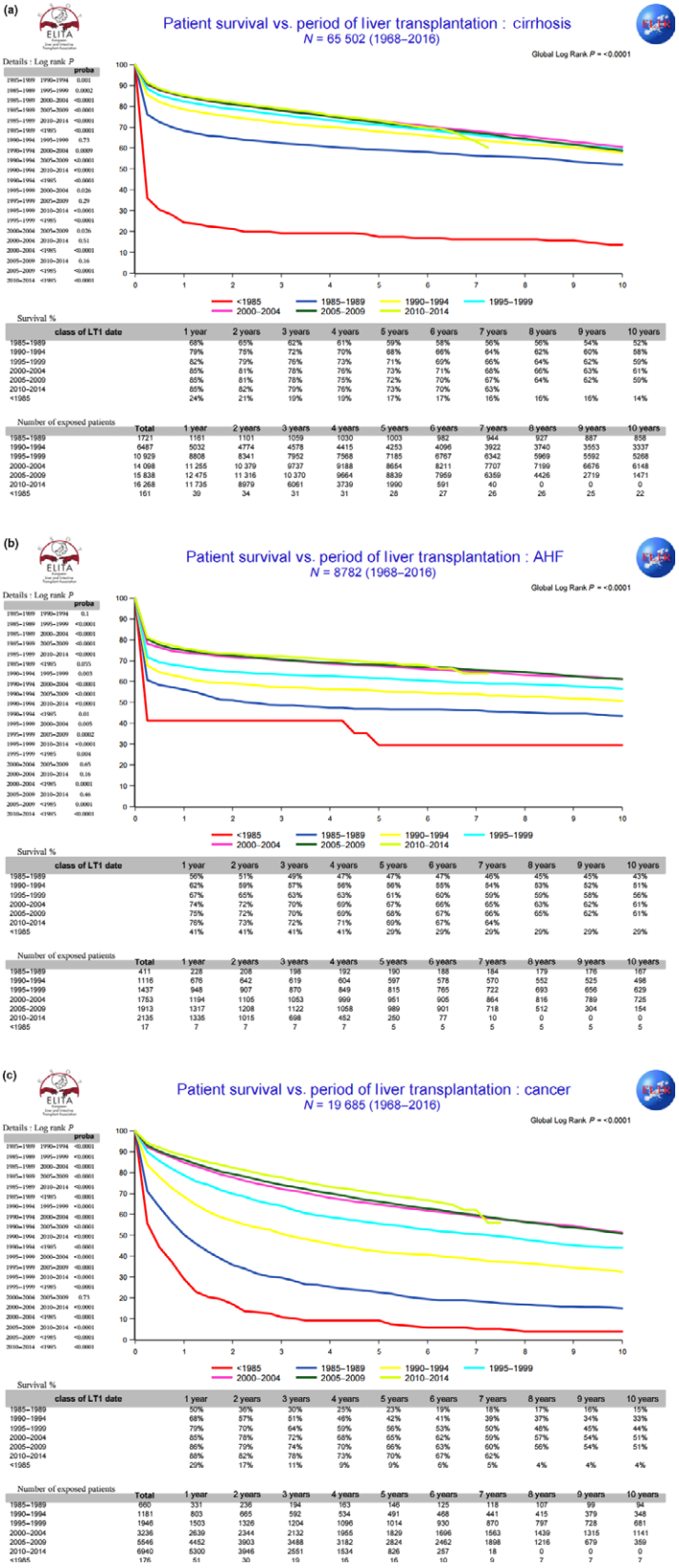


Figure 5 Patient survival versus period of liver transplantation: (a) Cirrhosis, n = 65 502 (1968–2016), (b) AHF, n = 8782 (1968–2016). (c) Cancer, n = 19 685 (1968–2016).

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41% at 20 years. After an improvement between 1985 and 2000, the survival of patients appears to be relatively steady since 2000 (Fig. 4).

The improvement in survival was seen in patients transplanted for all the three main indications; cirrhosis (Fig. 5a), fulminant hepatitis (Fig. 5c) but was particularly regular in LT for cancers (Fig. 5c). The 5-year patient survival rate was significantly better for cirrhosis (71%) than for primary liver tumors (64%, $P < 0.001$) and acute hepatic failure (65%, $P < 0.001$). HBV and HCV co-infection had a better 5-year survival (80%) compared with mono-infection with HCV (64%) or HBV (74%). The better 5-year survival rates obtained in metabolic diseases (79%), cholestatic disease (79%), and congenital biliary disease (85%), are partly explained by the high percentage of children in these groups. The survival rates in adults and children were, respectively, 76% and 85% for metabolic diseases, 79% and 86% for cholestatic disease, and 82% and 85% for congenital biliary disease. The details of survival rates at 1, 5 and 10, 15 and 20 years according to the primary indication are listed in Table 1.

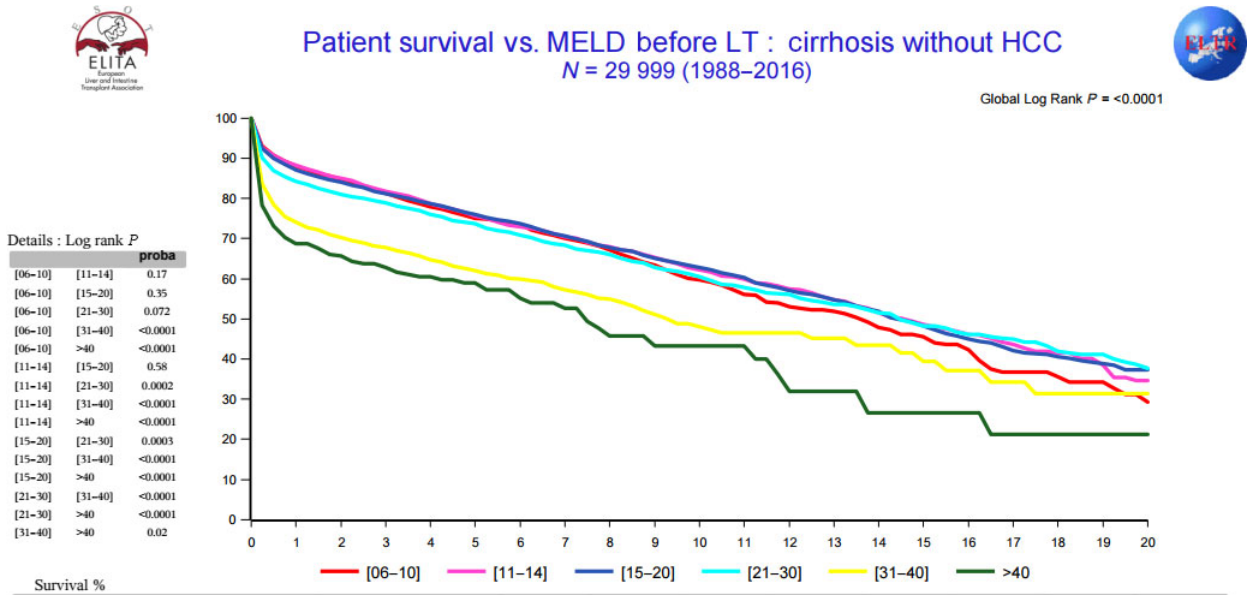
Although the 5-year survival improved in the 15 recent years for all the indications, the most important gain in survival was observed in LT for primary liver tumors (67%), liver metastases (61%), and acute liver failure (69%).

Since the adoption of the transplantation Model for End-stage Liver Disease (MELD) score in the majority of European countries in 2006–2007, the proportion of patients with a high MELD score (>30) at transplant has almost doubled. However, the survival of these patients is less optimal, especially for those with a MELD score at transplant higher than 40 (Fig. 6).

Survival according to donor and recipient characteristics

Donor characteristics

The majority of donors were male (57%). Fifty-eight percent were younger than 50 years, whereas 23% were older than 60 years. A gradual increase in the percentage of livers coming from septuagenarian donors was



Details : Log rank *P*

		proba
[06–10]	[11–14]	0.17
[06–10]	[15–20]	0.35
[06–10]	[21–30]	0.072
[06–10]	[31–40]	<0.0001
[06–10]	>40	<0.0001
[11–14]	[15–20]	0.58
[11–14]	[21–30]	0.0002
[11–14]	[31–40]	<0.0001
[11–14]	>40	<0.0001
[15–20]	[21–30]	0.0003
[15–20]	[31–40]	<0.0001
[15–20]	>40	<0.0001
[21–30]	[31–40]	<0.0001
[21–30]	>40	<0.0001
[31–40]	>40	0.02

Survival %

Meld_class num	1 year	3 years	5 years	8 years	10 years	12 years	14 years	16 years	18 years	20 years
[06–10]	88%	81%	75%	67%	60%	53%	48%	42%	36%	29%
[11–14]	88%	82%	76%	68%	62%	57%	52%	46%	42%	35%
[15–20]	87%	81%	76%	68%	63%	57%	52%	45%	41%	37%
[21–30]	84%	79%	74%	66%	61%	56%	52%	46%	42%	38%
[31–40]	74%	68%	62%	55%	48%	46%	44%	37%	31%	31%
>40	69%	63%	59%	46%	43%	32%	27%	27%	21%	21%

Number of exposed patients

	Total	1 year	3 years	5 years	8 years	10 years	12 years	14 years	16 years	18 years	20 years
[06–10]	3240	2246	1480	1076	606	374	230	120	63	29	13
[11–14]	6347	4544	3082	2159	1235	769	528	349	203	98	40
[15–20]	9856	6945	4633	3204	1661	992	697	483	290	165	64
[21–30]	7302	5042	3224	2050	981	496	325	244	164	100	38
[31–40]	2896	1807	1108	693	214	62	35	22	15	8	6
>40	358	206	121	72	24	16	7	5	5	4	1

Figure 6 Patient survival versus MELD before LT: cirrhosis without HCC, *N* = 29 999 (1988–2016).

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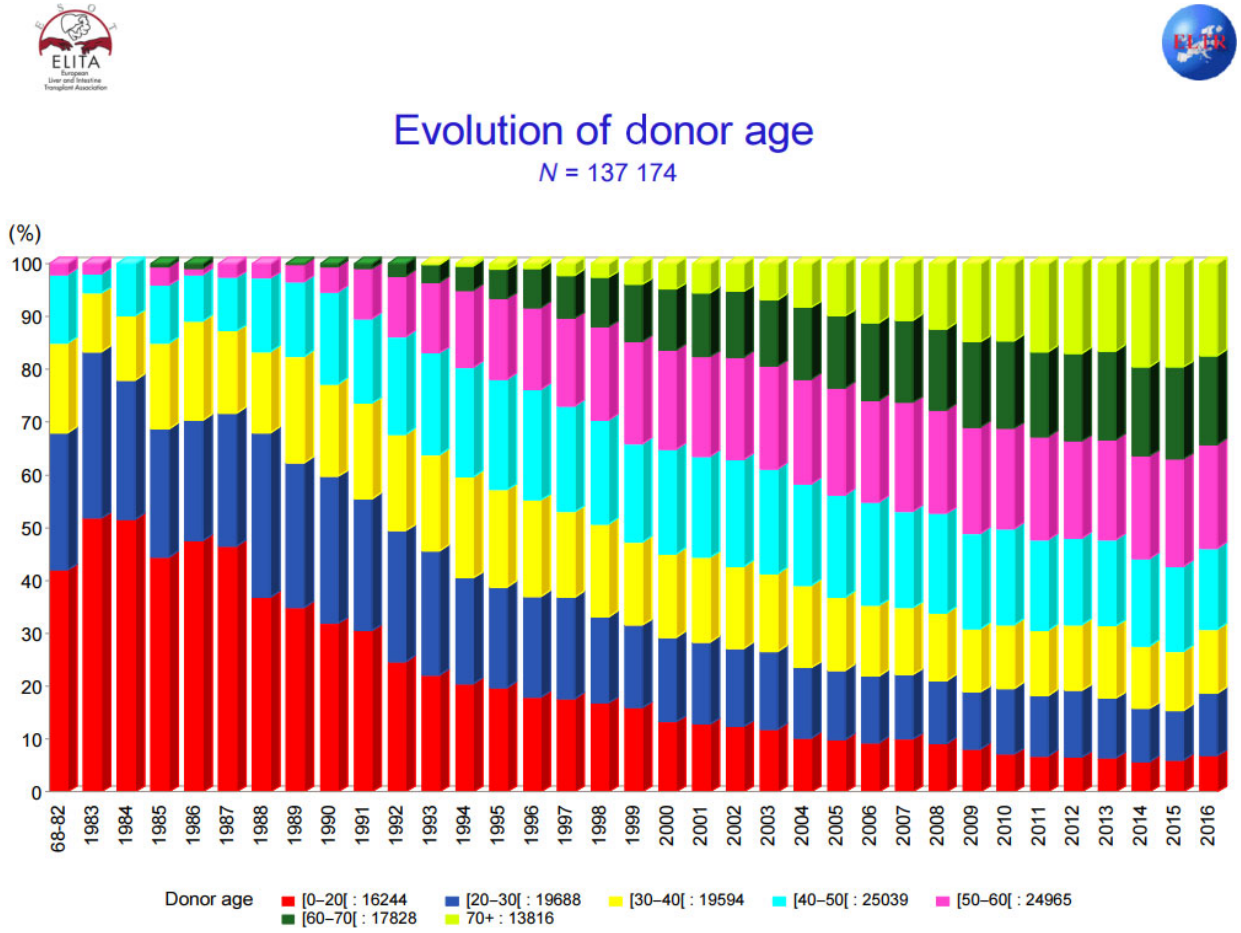


Figure 7 Evolution of donor age, *N* = 137 174.

observed (1% in 1993, 10% in 2005 and 20% in 2015) in relation to the increasing gap between a growing waiting list and a relatively stable donor pool (Fig. 7). Graft survival when organs were procured from donors younger than 55 years was significantly better than that with organs from donors older than 65 years (67% vs. 60% at 5 years, $P < 0.0001$) (Fig. 8). However, attention should be paid to the donor to recipient matching to interpret these results, older donor livers being more frequently transplanted to older recipients.

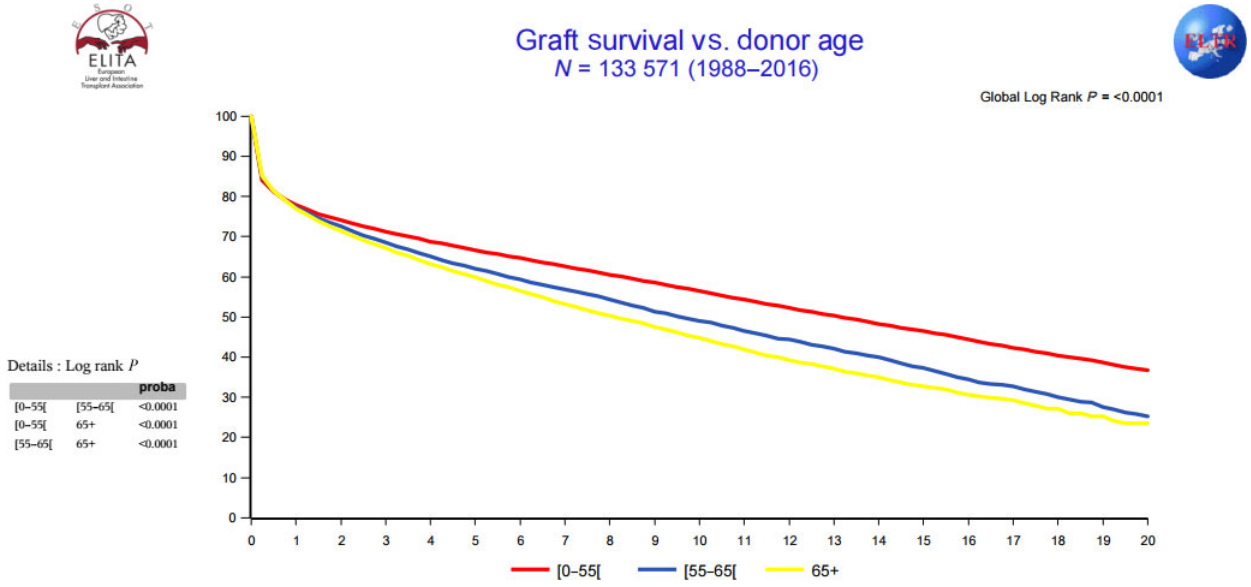
Recipient age

In addition to the better 5-year survival of pediatric versus adult LT recipients (90% vs. 81%, $P < 0.0001$), an influence of age was noted for adult recipients. Survival rates were 75% for adults aged 18–45 years, 71% for 46–60 years, 65% for 60–70 years, and 60% for septuagenarians. However, average age of transplanted recipients has increased steadily during the last decade, and patients older than 60 years, who represented <5% in the 1980s, currently represent more than 30% of transplant recipients (Fig. 9). Older grafts are more frequently transplanted to older recipients. Septuagenarian recipients received 43% grafts older than 60-years and only 12% of grafts younger than 30-years, explaining at least in part, the difference in survival between recipient age groups (Fig. 10). Importantly, LT offered a 10-year survival up to 40% in septuagenarians.

Blood group compatible and incompatible transplants

In elective conditions, 93% of LTs were isogroup, and 6.5% were compatible, whereas in emergency, 3% of LT were incompatible. In both elective and emergency conditions, isogroup LTs had a better 5-year survival compared with compatible or incompatible LTs (66% vs. 62% vs. 57%, $P < 0.0001$) and (56% vs. 53% vs. 28%, $P = 0.001$) respectively. However, the use of these incompatible grafts in emergency indications allows a 38% survival rate at 1 year in patients otherwise expected to have a fatal outcome.

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Survival %

3 class Donor age	1 year	3 years	5 years	8 years	10 years	12 years	14 years	16 years	18 years	20 years
[0–55[	78%	71%	67%	61%	56%	52%	48%	44%	40%	37%
[55–65[	77%	68%	62%	54%	49%	44%	40%	35%	30%	25%
65+	77%	67%	60%	50%	45%	39%	35%	31%	27%	24%

Number of exposed patients

	Total	1 year	3 years	5 years	8 years	10 years	12 years	14 years	16 years	18 years	20 years
[0–55[	90 613	61 718	47 602	38 474	26 870	20 618	15 293	10 929	7399	4610	2683
[55–65[	21 238	14 128	9969	7337	4497	3064	1956	1191	623	303	142
65+	21 720	13 916	8869	5765	2793	1704	932	484	222	83	24

Figure 8 Graft survival versus donor age, *n* = 133 571 (1988–2016).

Survival according to surgical technique

Auxiliary grafts represented 0.5% of overall LTs with a similar graft survival as compared with nonauxiliary grafts in urgent (5-year survival rates: 57% vs. 56%), and elective (66% vs. 69%) indications. The shorter the ischemia time; the better was the graft survival. Five-year survival was 70% for ischemia time <6 h, 67% for 6–12 h, 63% for 12–15 h, and 58% for >15 h. The use of static graft preservation solutions evolved during three distinct periods: period 1 before 1990 with the main use of Collins solution; period 2 between 1990 and 2000 with the almost exclusive use of UW (University of Wisconsin); period 3 after 2000 with an increasing use of new solutions with different characteristics such as HTK, Celsior, IGL 1 or SCOT (Fig. 11). Overall graft survival at 5 years for the main solutions was 74% for Celsior and IGL 1, 72% for UW and 69% for HTK (Fig. 12). If only partial livers were considered, survival was 83% for IGL 1, 79% for Celsior, 77% for UW, and 71% for HTK.

Alternative procedures to LT using full size livers from donors after brain death (DBD) have been increasingly used in recent years. While representing <10% before 2000 they concerned more than 20% of overall LT procedures after 2000 and 75% in pediatrics. A differentiation between adult and pediatric patients is necessary; because alternative techniques are used differently in each population and the patient's outcome may differ.

Adult population

Before 1994, alternative procedures concerned mainly reduced and split livers. Domino grafts were introduced in 1994 and living donation in 1996. Donation after cardiac death (DCD) was introduced in 2001 and since then, has gradually increased to represent currently almost 40% of the alternative procedures in adults. Consequently, the proportion of split, living, reduced, and domino grafts has decreased. The latter two modalities are really associated with the more significant decrease (Fig. 13a). Ten-year graft survivals for each type of graft are summarized in Fig. 13b. Survival at 5 years was similar between DBD full size grafts, split liver, domino, and DCD (66% to 67%), but higher than that of reduced grafts and living donors (63% in both).

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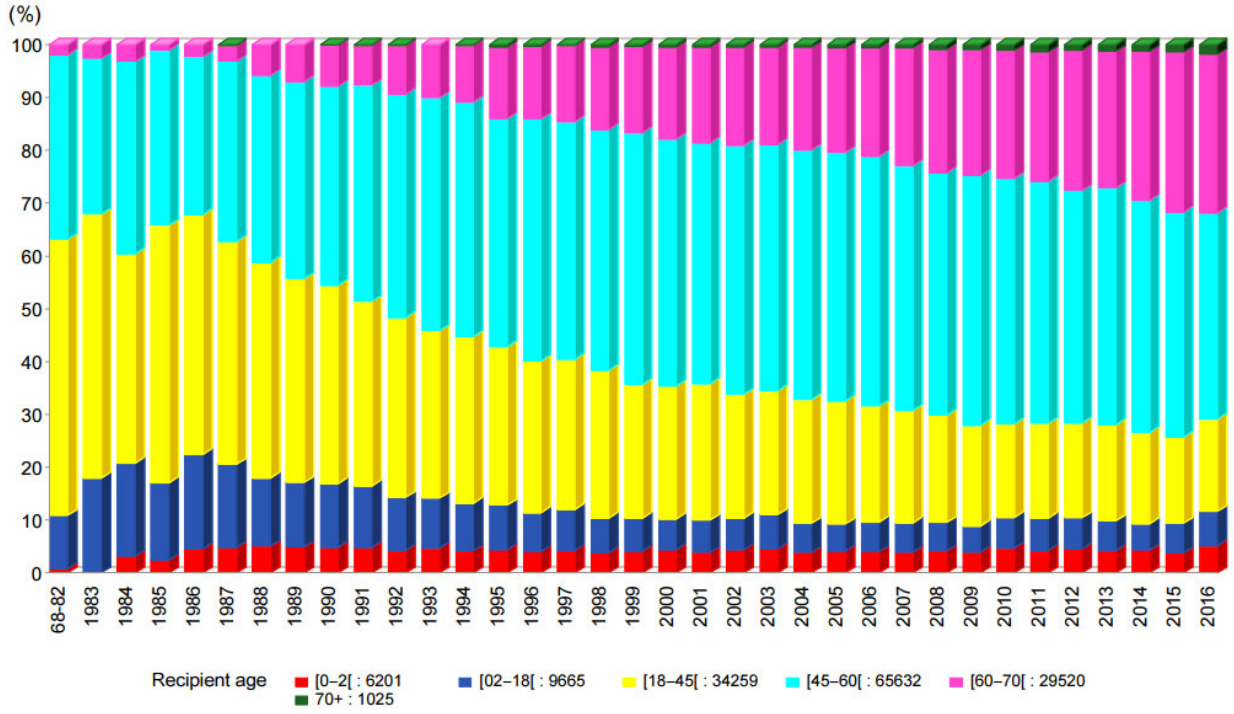


Figure 9 Evolution of recipient age, *N* = 146 302.

Pediatric population

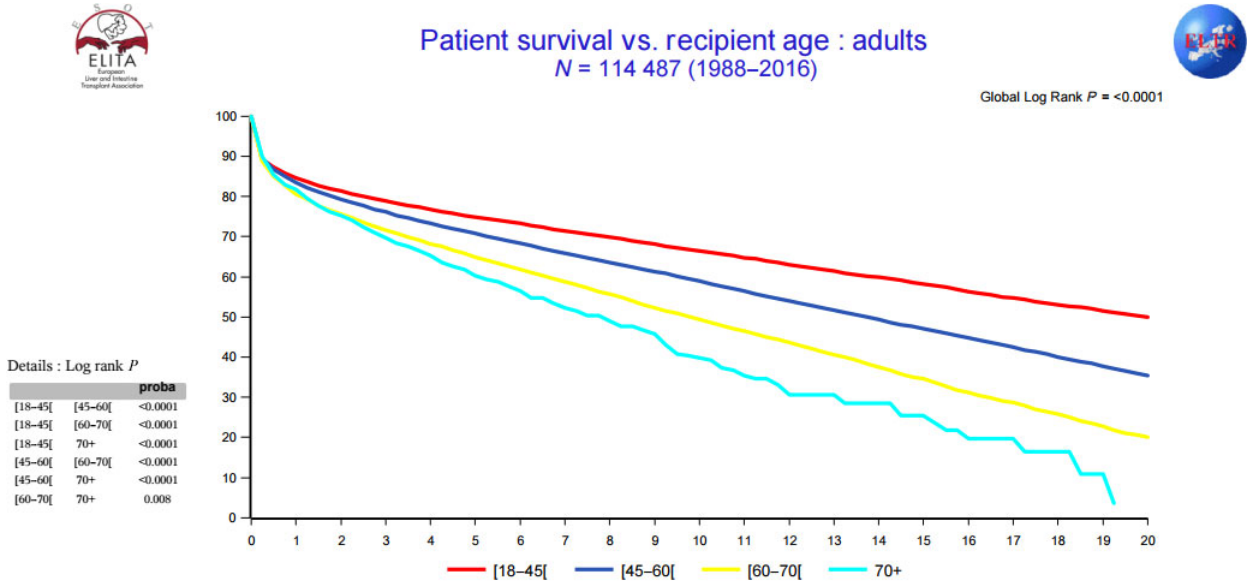
Before 1988, alternative procedures concerned mainly reduced livers. Split livers were introduced in 1988 and living donation in 1991 and since their introduction both have gradually increased to represent currently more than 90% of the alternative procedures in children (Fig. 14a). Ten-year graft survivals for each type of graft are summarized in Fig. 14b. Survival at 5 years was similar between DCD and living donors (80% and 78%, respectively), but higher than that of DBD full size grafts, split liver, and reduced grafts (74%, 71%, and 65% respectively). Domino transplant is rarely used in pediatric patients.

Mortality after LT

While 1 year patient survival was 81% between 1995 and 1999, it has dramatically improved to reach 86% after 2010 (Fig. 4). The critical period for post-LT outcome is represented by the first year: 46% of deaths and 67% of re-LT occur within the first year after LT (Fig. 15). In 44% of cases, re-LT is indicated in the month after primary LT, and more than a half (59%) of patients who die, do so within the 6 months after LT.

Data represented in Fig. 16 correspond to the distribution of main causes of death according to the time of their incidence. Main causes of death in the 28 637 patients who died after primary LT or Re-LT were differently distributed. Whereas death from primary graft nonfunction or dysfunction, infections, and technical (biliary or vascular) complications were more frequent within the first 6 months post-LT, tumor or nontumor recurrence and tumor *de novo* were more frequent after the first month. Interestingly, the proportion of tumor and nontumor recurrences as a cause of death is decreasing during the last years.

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Details : Log rank *P*

		proba
[18–45[	[45–60[	<0.0001
[18–45[	[60–70[	<0.0001
[18–45[	70+	<0.0001
[45–60[	[60–70[	<0.0001
[45–60[	70+	<0.0001
[60–70[	70+	0.008

Survival %

Age of Recipient	1 year	3 years	5 years	8 years	10 years	12 years	14 years	16 years	18 years	20 years
[18–45[	85%	79%	75%	70%	66%	63%	60%	56%	53%	50%
[45–60[	84%	76%	71%	64%	59%	54%	49%	45%	40%	35%
[60–70[	81%	72%	65%	56%	49%	44%	37%	31%	26%	20%
70+	82%	70%	60%	49%	40%	31%	28%	20%	16%	

Number of exposed patients

	Total	1 year	3 years	5 years	8 years	10 years	12 years	14 years	16 years	18 years	20 years
[18–45[	28 366	21 006	16 636	13 820	10 188	8181	6370	4910	3648	2561	1728
[45–60[	58 246	42 471	31 927	25 149	17 064	12 837	9258	6496	4333	2669	1549
[60–70[	26 938	18 351	12 719	9267	5460	3758	2526	1554	867	449	219
70+	937	611	370	243	109	69	34	21	9	4	0

Figure 10 Patient survival versus recipient age: adults *N* = 114 487 (1988–2016).

Re-transplantation

Five-year graft survival rates following a second and a third LTs were 48% and 42%, respectively, significantly lower than those for primary LT (66% – $P < 0.0001$) (Fig. 17).

Re-LT was indicated in 8482 cases mainly for primary nonfunction, technical complications (biliary or vascular), and rejection within the first month post-LT. Tumor or nontumor recurrences and *de novo* tumor were more frequent after the first month (Fig. 18). Late re-LT, more than 1 month after the first LT, has a significantly better graft survival than early re-LT performed within the month after the first LT (50% vs. 45% at 5 years, $P < 0.0001$) (Fig. 19). Re-LT which is mostly used in young patients (Fig. 3a) has declined during the last decade (Fig. 3b). Interestingly, tumor causes and nontumor recurrence are decreasing during the last years, whereas technical complications, primary graft nonfunction or dysfunction and infection are increasing.

Waiting time

When more than 90% of candidates waited <3 months in the 1980s, they represented 70% in the 1990s and slightly more than a half since 2000. This evolution is likely because of three main reasons: the increase in the number of candidates for transplantation following the advent of more and more effective immunosuppressive treatments, the scarcity of grafts and the use of the MELD which gives priority to the sickest candidates. The 5-year survival of patients who have spent <3 months on the waiting list, certainly because they were more severe, was 70%, 5% lower than that of all the other groups of waiting times in the list ($P < 0.0001$).

Discussion

The ELTR data provide a descriptive overview of the overall situation of LT in Europe. There is of course heterogeneity in the policies in the 29 contributing countries. This manuscript summarizes the results as

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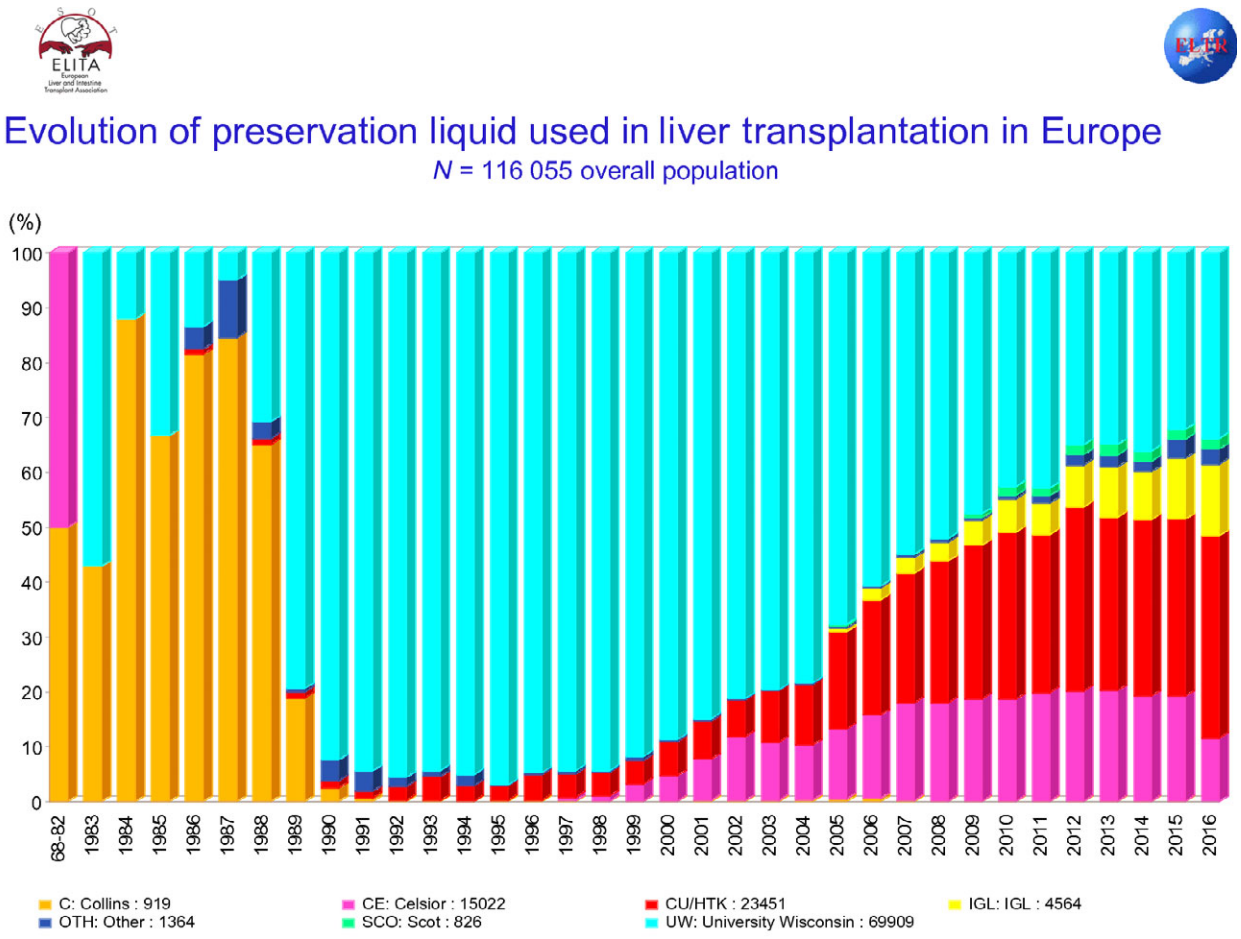


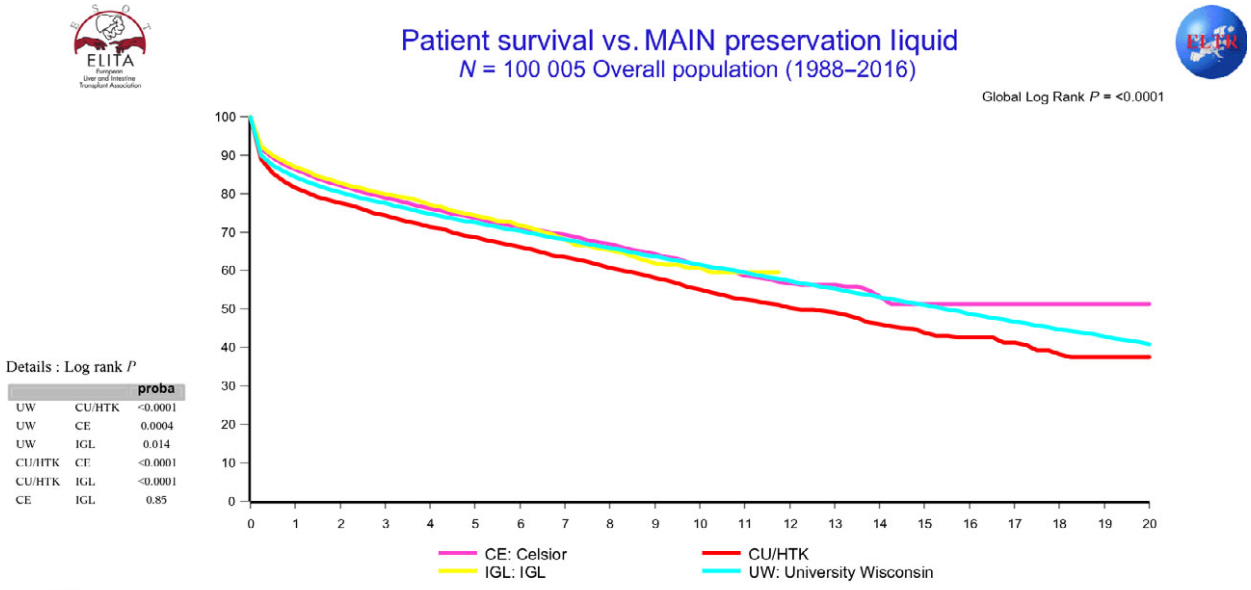
Figure 11 Evolution of preservation liquid used in liver transplantation in Europe, *n* = 116 055 overall population.

a whole, and represents a kind of freeze-frame rather than a generalized statement for Europe. At the same time, the ELTR remains the unique entity capable of providing such statistics, capable of giving a global snapshot of the European experience, and helping to identify important trends that may guide further practice.

Liver transplantation has become the best, if not the only effective treatment for severe irreversible liver disease. More than 7000 LTs are performed annually in Europe, and the results look satisfactory at 5 years (71% survival) with still a room for improvement at long-term (61% at 10 years and 41% at 20 years). The demand far exceeds the availability of organs for transplantation. It is therefore essential to continue to promote organ donation in Europe in order to avoid mortality on the waiting list, and a "drastic" selection of candidates. By allowing the transplant of the sickest candidates first, the MELD score has dramatically decreased the risk of death on the waiting list. However, the post-LT survival of high MELD score patients is less optimal, mostly for those with MELD score at transplant higher than 40. It also appears essential to continue to improve the perioperative management of LT at all levels, along with a better prevention of long-term complications. The data provided by the ELTR are a basis to target the timing, and fields to improve the results.

The main indication for LT is cirrhosis with end stage liver disease. However, its proportion is decreasing continuously as compared with HCC. Fulminant hepatitis of unknown cause is also declining. Such relative diminution of cirrhosis is mainly related to the accelerated decline in HCV indications as a result of effective direct-acting antiviral drugs [17]. Thus, hundreds of liver grafts every year are becoming available for indications other than HCV. Even though NASH related cirrhosis is still less frequent in Europe compared with the US, it is anticipated to become the leading indication for LT within the next decade.

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Details : Log rank *P*

		proba
UW	CU/HTK	<0.0001
UW	CE	0.0004
UW	IGL	0.014
CU/HTK	CE	<0.0001
CU/HTK	IGL	<0.0001
CE	IGL	0.85

Survival %

preserv_liq_c	1 year	3 years	5 years	8 years	10 years	12 years	14 years	16 years	18 years	20 years
UW: University Wisconsin	84%	77%	72%	66%	62%	57%	53%	49%	45%	41%
CU/HTK	82%	74%	69%	61%	55%	50%	46%	43%	38%	37%
CE: Celsior	86%	79%	74%	67%	61%	57%	53%	51%	51%	51%
IGL: IGL	87%	80%	74%	65%	61%					

Number of exposed patients

	Total	1 year	3 years	5 years	8 years	10 years	12 years	14 years	16 years	18 years	20 years
UW: University Wisconsin	61 288	46 592	37 560	30 864	21 906	16 781	12 273	8669	5775	3493	1878
CU/HTK	21 027	12 826	7287	4613	1897	912	425	223	108	42	31
CE: Celsior	13 544	9339	5797	3718	1548	703	275	85	4	3	1
IGL: IGL	4146	2722	1587	853	261	63	0	0	0	0	0

Figure 12 Patient survival versus main preservation liquid, *n* = 100 005 overall population (1988–2016).

In terms of results, all the indications have shown an improvement of survival especially HCC, mainly because of a better selection of patients, and the increasing effectiveness of down-staging techniques [18]. The ELTR cohort of patients has also established that some rare malignant tumors like hepatic hemangiosarcoma should be considered absolute contraindications for LT [19], while others like hereditary hemorrhagic telangiectasia [8] or hepatic epithelioid hemangio-endothelioma represent a good indication even in the presence of limited extrahepatic disease [12,24].

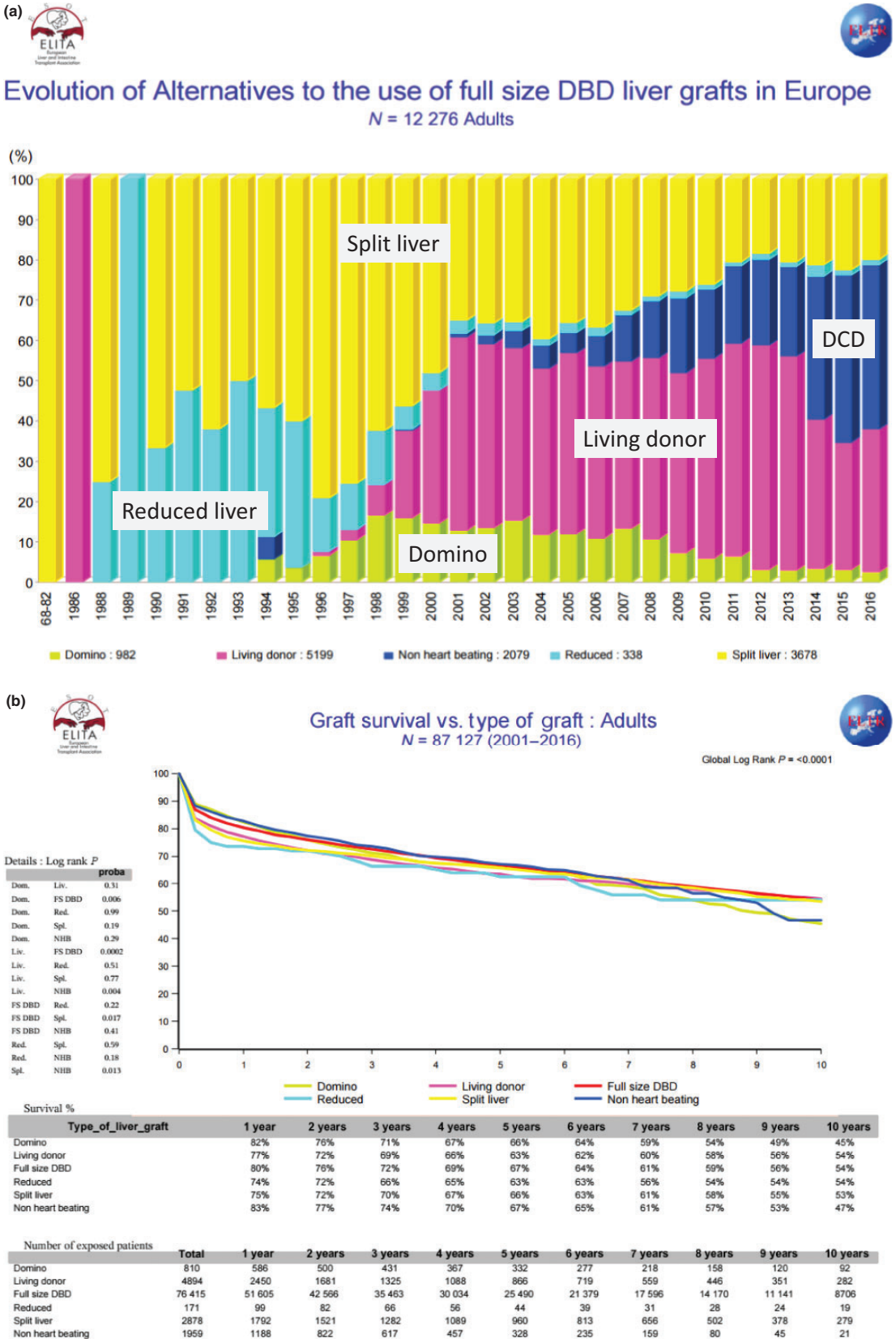
The average age of transplanted recipients has increased steadily during the last decade and a third of patients transplanted nowadays are >60 years. Noteworthy, LT can offer a 10 additional year benefit to 40% of septuagenarians. Also, an increasing number of transplanted liver grafts are coming from older donors with in most cases, the application of the old-to-old rule concerning the donor to recipient matching.

Alternatives to the conventional DBD full size graft are increasingly used in Europe. Split liver and living donation are increasingly used both in adult and pediatric LT, and DCD grafts are mostly used in adults with quite good survival results. Domino and reduced livers seem to be gradually disappearing. Optimization of donor management and organ preservation, offers the most realistic way to improve both the quality and pool of current organs. While only UW solution was used before 2000, an increasing number of new solutions are available today; the choice in preservation solution may have an independent impact on graft survival [25].

Also, while the introduction of cyclosporine and more recently Tacrolimus optimized immunosuppressive protocols, there is still room for improvement as recently shown by the use of prolonged release tacrolimus [26].

As a cause of graft loss, technical complications, primary graft nonfunction or dysfunction and infection are increasing, relatively. This could be related to the increasing use of marginal grafts coming from expanded donor criteria. Conversely, *de novo* tumor and nontumor recurrence as cause of graft loss or mortality are decreasing during the last years.

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Details : Log rank *P*		proba
Dom.	Liv.	0.31
Dom.	FS DBD	0.006
Dom.	Red.	0.99
Dom.	Spl.	0.19
Dom.	NHB	0.29
Liv.	FS DBD	0.0002
Liv.	Red.	0.51
Liv.	Spl.	0.77
Liv.	NHB	0.004
FS DBD	Red.	0.22
FS DBD	Spl.	0.017
FS DBD	NHB	0.41
Red.	Spl.	0.59
Red.	NHB	0.18
Spl.	NHB	0.013

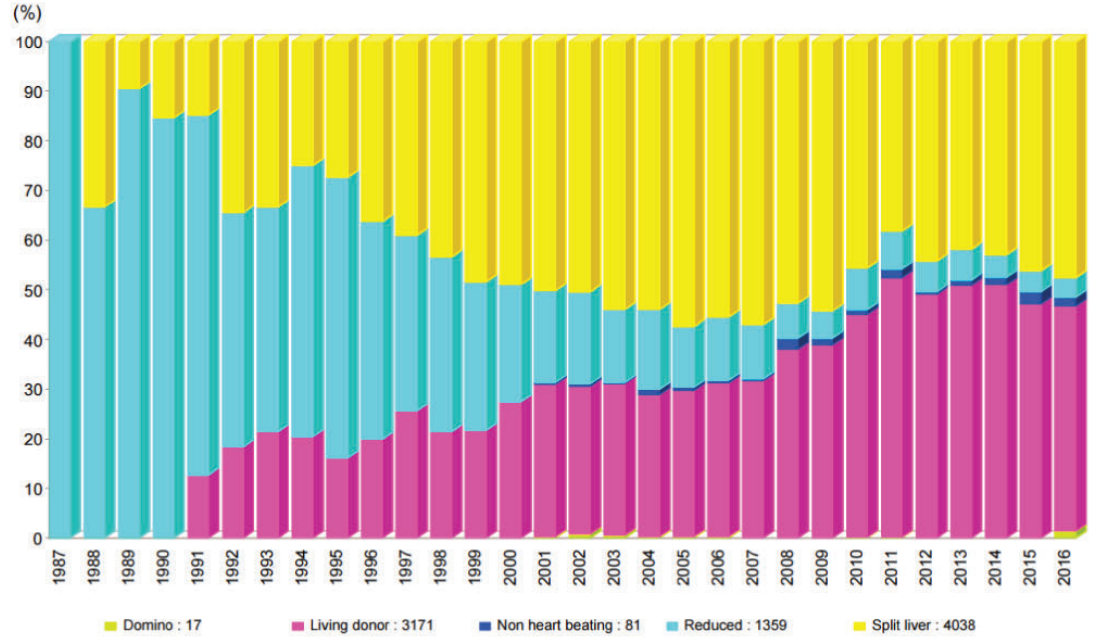
Survival %									
Type_of_liver_graft	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
Domino	82%	76%	71%	67%	66%	64%	59%	54%	49%	45%
Living donor	77%	72%	69%	66%	63%	62%	60%	58%	56%	54%
Full size DBD	80%	76%	72%	69%	67%	64%	61%	59%	56%	54%
Reduced	74%	72%	66%	65%	63%	63%	56%	54%	54%	54%
Split liver	75%	72%	70%	67%	66%	63%	61%	58%	55%	53%
Non heart beating	83%	77%	74%	70%	67%	65%	61%	57%	53%	47%

Number of exposed patients	Total	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
Domino	810	586	500	431	367	332	277	218	158	120	92
Living donor	4894	2450	1681	1325	1088	866	719	559	446	351	282
Full size DBD	76 415	51 605	42 566	35 463	30 034	25 490	21 379	17 596	14 170	11 141	8706
Reduced	171	99	82	66	56	44	39	31	28	24	19
Split liver	2878	1792	1521	1282	1089	960	813	656	502	378	279
Non heart beating	1959	1188	822	617	457	328	235	159	80	45	21

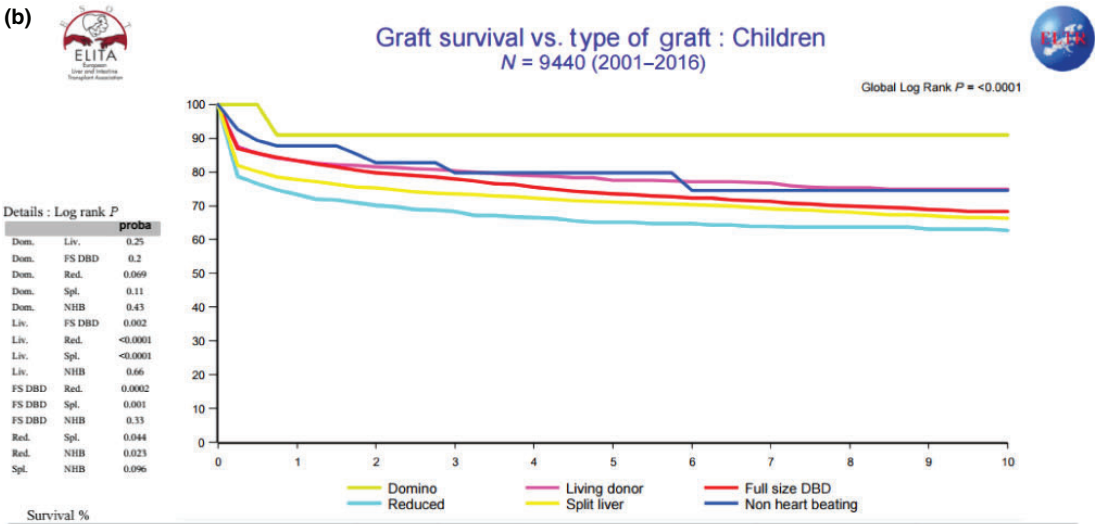
Figure 13 (a) Evolution of alternatives to the use of full size donors after brain death (DBD) liver grafts in Europe, *n* = 12 276 adults. (b) Graft survival versus type of graft: Adults, *N* = 87 127 (2001–2016).

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(a)



(b)



Details : Log rank *P*

		proba
Dom.	Liv.	0.25
Dom.	FS DBD	0.2
Dom.	Red.	0.069
Dom.	Spl.	0.11
Dom.	NHB	0.43
Liv.	FS DBD	0.002
Liv.	Red.	<0.0001
Liv.	Spl.	<0.0001
Liv.	NHB	0.66
FS DBD	Red.	0.0002
FS DBD	Spl.	0.001
FS DBD	NHB	0.33
Red.	Spl.	0.044
Red.	NHB	0.023
Spl.	NHB	0.096

Survival %

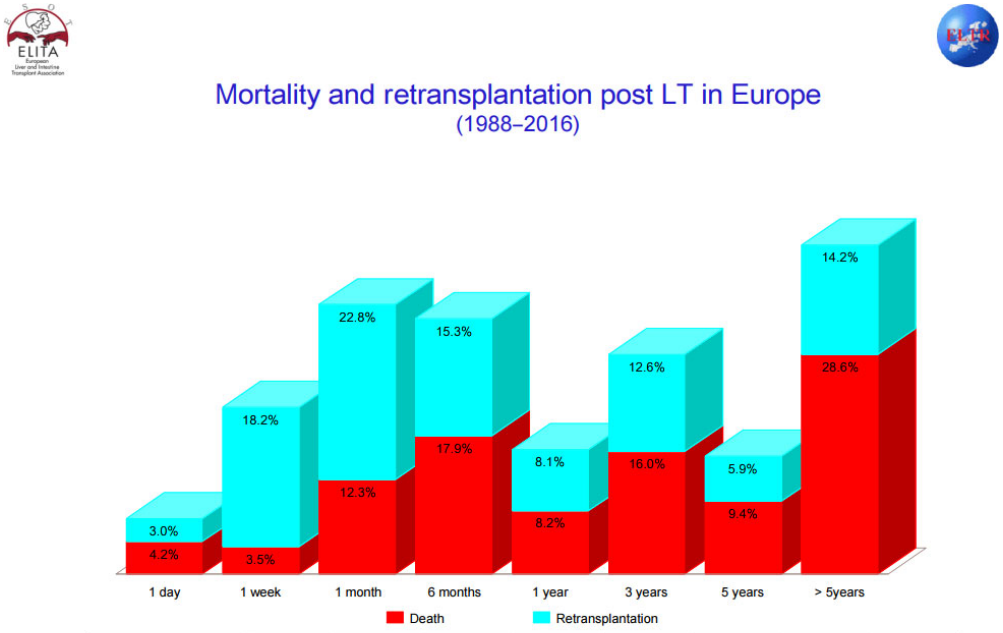
Type_of_liver_graft	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
Domino	91%	91%	91%	91%	91%	91%	91%	91%	91%	91%
Living donor	83%	82%	80%	79%	78%	77%	77%	75%	75%	75%
Full size DBD	83%	80%	78%	75%	74%	72%	71%	70%	69%	68%
Reduced	73%	70%	68%	66%	65%	65%	64%	64%	63%	63%
Split liver	78%	75%	74%	72%	71%	70%	69%	68%	67%	66%
Non heart beating	88%	83%	80%	80%	80%	75%	75%	75%	75%	75%

Number of exposed patients

	Total	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
Domino	17	9	3	3	3	3	2	2	2	1	1
Living donor	2710	1518	1178	942	783	640	527	438	311	240	185
Full size DBD	2808	1936	1591	1332	1125	966	836	702	570	468	375
Reduced	594	391	348	309	272	239	206	186	166	139	115
Split liver	3241	2100	1759	1484	1277	1101	954	797	625	469	367
Non heart beating	70	45	31	26	20	19	14	11	7	5	4

Figure 14 (a) Evolution of alternatives to the use of full size donors after brain death (DBD) liver grafts in Europe, *N* = 8666 children. (b) Graft survival versus type of graft: children, *N* = 9440 (2001–2016).

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Cumulative proportions	1 day	1 week	1 month	6 months	1 year	3 years	5 years	>5 years
Death	4%	8%	20%	38%	46%	62%	71%	100%
Retransplantation	3%	21%	44%	59%	67%	80%	86%	100%

Figure 15 Mortality and retransplantation post LT in Europe (1988–2016).

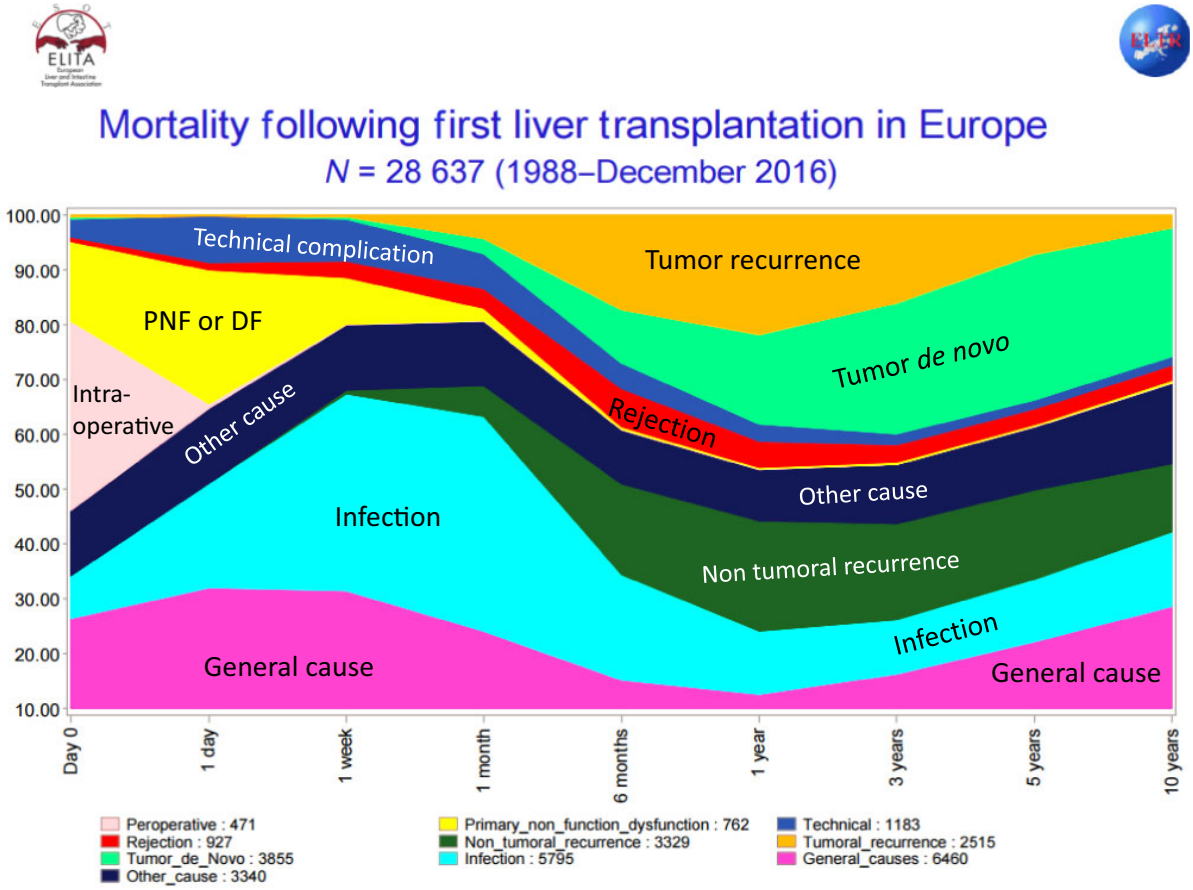
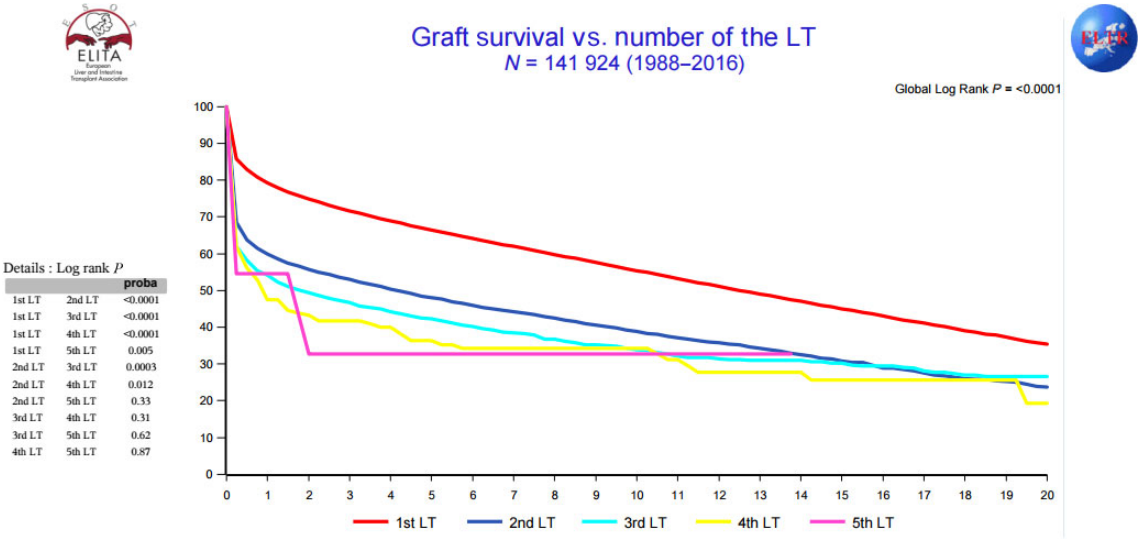


Figure 16 Mortality following first liver transplantation in Europe, *N* = 28 637 (1988-December 2016).

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Details : Log rank *P*

		proba
1st LT	2nd LT	<0.0001
1st LT	3rd LT	<0.0001
1st LT	4th LT	<0.0001
1st LT	5th LT	0.005
2nd LT	3rd LT	0.0003
2nd LT	4th LT	0.012
2nd LT	5th LT	0.33
3rd LT	4th LT	0.31
3rd LT	5th LT	0.62
4th LT	5th LT	0.87

Survival %

Rang Th	1 year	3 years	5 years	8 years	10 years	12 years	14 years	16 years	18 years	20 years
1st LT	79%	72%	66%	60%	55%	51%	47%	43%	39%	35%
2nd LT	60%	53%	48%	42%	39%	36%	33%	29%	26%	24%
3rd LT	54%	47%	42%	37%	34%	31%	31%	29%	27%	27%
4th LT	47%	42%	36%	34%	34%	28%	28%	26%	26%	19%
5th LT	55%	33%	33%	33%	33%	33%				

Number of exposed patients

	Total	1 year	3 years	5 years	8 years	10 years	12 years	14 years	16 years	18 years	20 years
1st LT	128056	87625	64997	50956	34364	25974	19044	13594	9281	5944	3611
2nd LT	12241	6495	4749	3653	2437	1809	1304	923	618	407	265
3rd LT	1447	696	505	391	276	218	175	131	100	65	39
4th LT	169	71	50	36	27	24	16	13	6	5	3
5th LT	11	5	2	1	1	1	1	0	0	0	0

Figure 17 Graft survival versus number of the LT, *N* = 141 924 (1988–2016).

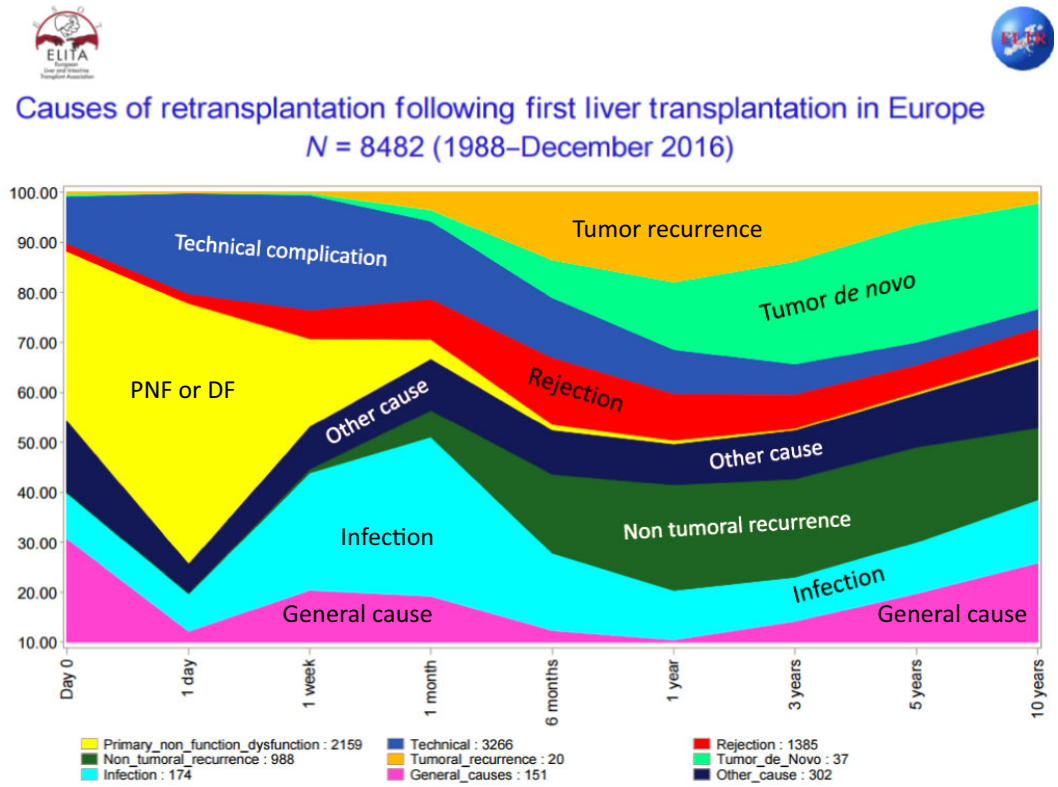
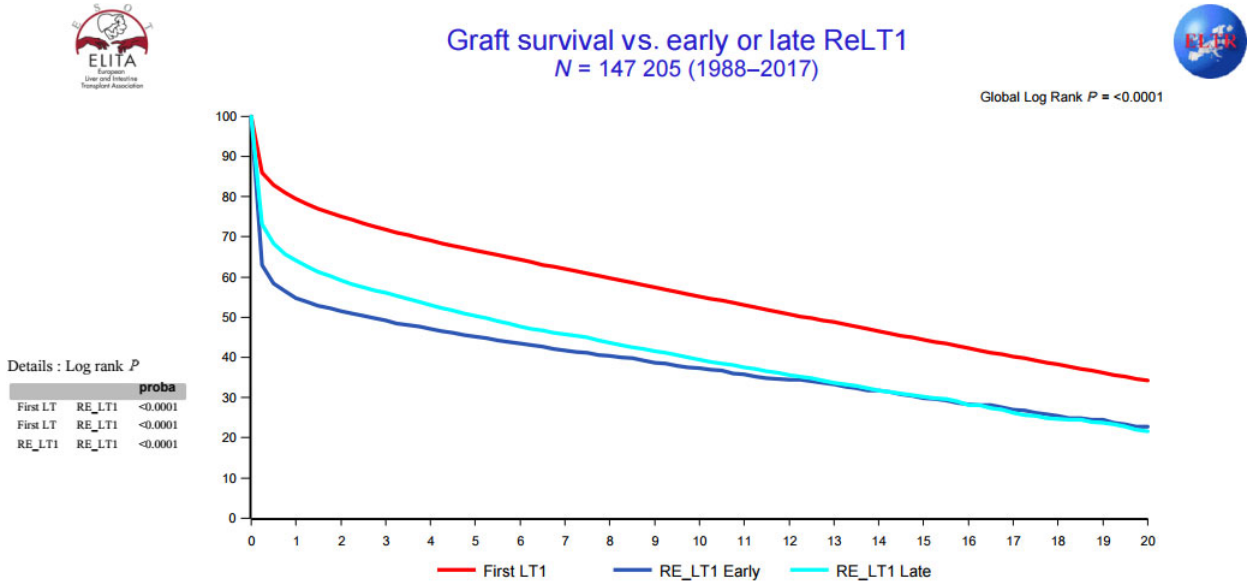


Figure 18 Causes of retransplantation following first liver transplantation in Europe, *N* = 8482 (1988-December 2016).

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Survival %

Rang_TH	1 year	3 years	5 years	8 years	10 years	12 years	14 years	16 years	18 years	20 years
First LT1	79%	72%	67%	60%	55%	51%	47%	42%	38%	34%
RE_LT1 Early	55%	49%	45%	40%	37%	34%	32%	28%	25%	23%
RE_LT1 Late	64%	56%	50%	44%	39%	36%	32%	28%	25%	22%

Number of exposed patients

	Total	1 year	3 years	5 years	8 years	10 years	12 years	14 years	16 years	18 years	20 years
First LT1	134598	91280	67979	53467	36507	27557	20414	14645	10107	6596	4039
RE_LT1 Early	5579	2670	1998	1549	1044	779	563	410	285	187	131
RE_LT1 Late	7028	3928	2878	2199	1461	1083	778	539	355	239	149

Figure 19 Graft survival versus early or late ReLT1, *N* = 147 205 (1988–2017).

There are some limitations to our study. Data quality, reliability, and representativeness is an everyday concern for the ELTR since its creation in 1986. With this constantly in mind, the ELTR has implemented several procedures and adapted them all along the years to control the quality of data, from collection, to statistical analysis. However, biases may persist as for all observational studies; therefore, the interpretation of these descriptive data must be done with caution. Lost-to-follow-up (LTFU) patients are a real problem in the reported outcome. It is mainly related to the increasing number of transplanted patients who move to another place within a country or outside the country. More than 72% of ELTR data are shared with official OSOs who have setup a drastic tracking procedure to minimize the rate of LTFU. The remaining 28% who enter the data directly in our platform are regularly invited to consult the dynamically updated list of queries to solve all discrepancies and to report a recent patient follow-up.

By the prospective evaluation of almost all patients transplanted in Europe since the last fifty years, the ELTR provides valuable data concerning the evolution of LT, the dynamic changes in indications, in donor and recipients profile, as well as in preservation, technical aspects and post-transplant management. These data can help refine the indications for transplant in rare diseases, and establish new guidelines, while targeting the real fields which need improvement in order to optimize the results of LT.

Authorship

RA, VK and VC: conception and design, acquisition of data, data analysis and interpretation of results, writing the first draft, critical revision, final approval. All the rest of co-authors: acquisition of data, critical revision, final approval.

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Conflicts of interest

The authors have declared no conflicts of interest.

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