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Liver transplantation with deceased ABO-incompatible donors is life-saving but associated with increased risk of rejection and post-transplant complications

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Summary

ABO-incompatible (ABOi) liver transplantation (LT) with deceased donor organs is performed occasionally when no ABO-compatible (ABOc) graft is available. From 1996 to 2011, 61 ABOi LTs were performed in Oslo and Gothenburg. Median patient age was 51 years (range 13–75); 33 patients were transplanted on urgent indications, 13 had malignancy-related indications, and eight received ABOi grafts for urgent retransplantations. Median donor age was 55 years (range 10–86). Forty-four patients received standard triple immunosuppression with steroids, tacrolimus, and mycophenolate mofetil, and forty-four patients received induction with IL-2 antagonist or anti-CD20 antibody. Median follow-up time was 29 months (range 0–200). The 1-, 3-, 5-, and 10-year Kaplan–Meier estimates of patient survival (PS) and graft survival (GS) were 85/71%, 79/57%, 75/55%, and 59/51%, respectively, compared to 90/87%, 84/79%, 79/73%, and 65/60% for all other LT recipients in the same period. The 1-, 3-, 5-, and 10-year GS for A_2 grafts were 81%, 67%, 62%, and 57%, respectively. In conclusion, ABOi LT performed with non-A_2 grafts is associated with inferior graft survival and increased risk of rejection, vascular and biliary complications. ABOi LT with A_2 grafts is associated with acceptable graft survival and can be used safely in urgent cases.

Introduction

Liver transplantation (LT) is the optimal and only available treatment for end-stage liver disease. The leading indications for urgent LT are acute liver failure, acute on chronic liver failure, and rescue transplantations resulting from graft nonfunction or complications not related to the transplantation procedure. ABO-incompatible (ABOi) LT is sometimes used as a rescue alternative when no ABO-compatible (ABOc) graft is available in urgent and critical cases.

In liver transplant programs in Western countries, the outcome after ABOi LT using deceased donors has been variable and in some cases disappointing, with poor graft function, early graft loss, and an increased rate of complica-

tions [1–11]. The indications for transplantation have been diverse, which has made consistent comparisons of these results difficult. However, LT with A_2 grafts to O recipients has results similar to those achieved with ABOc LT [12–15]. ABOi LT on an elective basis with living donor grafts has been well established in certain Asian countries, in particular in Japan where the availability of deceased organ donors is limited [16,17]. This experience has been transferred from ABOi kidney transplantation, with reported graft and patient survival comparable to what is achieved with ABO-compatible (ABOc) LT [16,18–22].

The aim of this retrospective study was to analyze the outcome of all ABOi LTs performed in Gothenburg, Sweden and Oslo, Norway between 1996 and 2011 for both urgent (n = 33) and on an nonurgent indications (n = 28). The primary endpoints of the study were patient survival (PS) and graft survival (GS). In addition, we also specifically aimed to investigate the rate of vascular and biliary complications as well as the incidence of acute cellular and humoral rejections. The outcome was compared to that of all other ABOc LTs performed in Gothenburg and Oslo in the same time period (n = 1372). Data on the latter group were obtained from the Nordic Liver Transplant Registry (NLTR group).

ABOi LT was the only option for a life-saving procedure in the urgent cases because these patients did not fulfill the criteria for an urgent donor call within the Scandiatransplant collaborative network for organ exchange and therefore ran a high risk of dying if having to wait for an ABOc graft. The indications for transplantation of patients who were not in urgent need varied, but most of the patients had cancer, with hepatocellular carcinoma as the predominant malignancy. Some patients were transplanted because of a long waiting time, and most of these patients received an A_2 graft.

Patients and methods

Between February 1996 and December 2011, a total of 61 patients underwent LT using ABOi grafts at Sahlgrenska University Hospital in Gothenburg, Sweden (n = 36) and Oslo University Hospital, Norway (n = 25). The study included all ABOi LTs performed in this period, and no ABOi LTs were excluded. Complete medical files of these patients were extracted from center-specific medical records. The main patient characteristics are given in Table 1. The study population consisted of 23 women and 38 men with a median age of 51 years (range 13–75). The main urgent indications for performing an ABOi LT among these patients were severe hepatic failure (acute or acute on chronic liver failure [n = 26, 43%]) and rescue LT after failure of an ABOc graft (n = 7, 11.5%). Cancer was the

Table 1. Patient characteristics.

Donor→recipient blood group	A_1→0	A_1→B	A_2→0	A_2→B	AB→A	AB→B	B→0	B→A	$ABOi_{total}$
Number of patients	11	2	31	1	2	1	12	1	61
Retransplantation*	2 (18.2%)		2 (6.5%)	1 (100%)			3 (25%)		8 (13.1%)
Proportion of male patients	4 (36.4%)	2 (100%)	21 (67.7%)	1 (100%)	2 (100%)	1 (100%)	6 (50%)	1 (100%)	38 (62.3%)
Patient age† (years)	50 (19–67)	37.5 (24–51)	51 (13–73)	37	42.5 (33–52)	75	53.5 (20–66)	57	51 (13–75)
Waiting time† (days)	3 (1–353)	1	38 (0–696)	1	5.5 (1–10)	49	14 (1–525)	86	
MELD score†	34 (10–40)	40	20 (6–40)	35	36.5 (33–40)	12	22 (6–40)	21	27 (6–40
Donor age (years)†	60 (22–73)	62 (59–65)	53 (10–86)	40	57 (55–59)	73	46 (22–70)	57	55 (10–86)
Main indication for ABOi LT									
Urgent indications									
ALF‡	6 (54.5%)	2 (100%)	3 (9.7%)		1 (50%)				12 (19.7%)
Acute on chronic	1 (9.1%)		9 (29.0%)		1 (50%)		3 (25%)		14 (23%)
Rescue-tx	2 (18.2%)		1 (3.2%)	1 (100%)			3 (25%)		7 (11.5%)
Nonurgent indications									
Cancer§	1 (9.1%)		8 (25.8%)				4 (33.3%)		13 (21.3%)
Long waiting time	1 (9.1%)		3 (9.7%)				2 (16.7%)		6 (9.8%)
Other			7 (22.6%)			1 (100%)		1 (100%)	9 (14.8%)

*ABOi LT represented a retransplantation.

†Numbers are presented as median and range.

‡Acute liver failure.

§6 cancer patients also qualify for "long waiting time" category.

main indication for nonurgent cases and was the indication in 13 patients (21.3%).

There was a wide range of Model for End-stage Liver Disease (MELD) scores among the patients. Median uncorrected MELD score was 27 (range 6–40). In 8 of the 61 cases, the ABOi LT represented a retransplantation following failure of a first ABOc graft; of these eight patients, seven were categorized as rescue transplantations. Median donor age was 55 years (range 10–86), and all were donations after brain death. Distribution of blood types of donors and recipients was as follows: $A_2 \rightarrow O$ $n = 31$, $B \rightarrow O$ $n = 12$, $A_1 \rightarrow O$ $n = 11$, $A_1 \rightarrow B$ $n = 2$, $AB \rightarrow A$ $n = 2$, $A_2 \rightarrow B$ $n = 1$, $AB \rightarrow B$ $n = 1$, and $B \rightarrow A$ $n = 1$. Sixty patients received a full graft, and one patient was given a right lobe graft from a split liver. The median waiting time was 18 days (range 0–696). One patient had a positive crossmatch before LT. Information regarding anti-HLA antibodies was available for 56 of 61 patients. Further details on patient characteristics and outcome are given in Table 2.

The study was approved by the local institutional and regional review board in Oslo (approval number 11/5852) and the regional ethics committee in Gothenburg (approval number 048-13).

Anti-A/B titers

For the majority of patients, anti-A/B immunoglobulin titers were measured at the time of LT and regularly thereafter for the first 4 weeks. The levels of IgM were tested using a saline technique while the levels of IgG were determined by indirect antiglobulin testing. Anti-A/B titers were determined as previously described [13].

Immunosuppressive regimen

Forty-four patients (72%) received a standard immunosuppressive regimen consisting of steroids, tacrolimus (trough target levels, 8–15 ng/ml), and mycophenolate mofetil. The immunosuppressive regimen used in the remaining 17 patients is given in Table 3. Of 61 patients, 44 (72%) were given induction therapy with IL-2 antagonist (basiliximab, 35 patients), anti-CD20 antibody (rituximab, 30 patients), or both (21 patients). Nine patients (15%) were treated with plasmapheresis (PP) or selective immunoadsorption (IA) (Glycosorb®, Glycorex Transplantation AB, Lund, Sweden) before LT. Twenty-eight (46%) received immunoglobulins (Kiovig® or Octagam®, 0.5 g/kg per dose).

The different immunosuppressive regimens used (Table 3) are the result of the heterogeneity in the patient population and differences in practice between the two participating centers. Furthermore, these LTs were performed over a relatively long period of time (1996–2011), during which there were changes in the immunosuppressive drugs.

Diagnosis of rejection

Rejection episodes were diagnosed based on a positive liver biopsy taken on clinical indication, a significant rise in liver enzymes, or both. Intact arterial and portal venous circulation in the liver graft was confirmed by duplex ultrasound in all cases. A Banff rejection activity index score of 3 or more was defined as positive for rejection. C4d staining of tissue samples were used for detection of antibody-mediated rejection (AMR).

Treatment of rejection

The primary treatment for rejection episodes was high-dose methylprednisolone according to protocol (1 g i.v. the first day, followed by 0.5 g on each of the consecutive 4 days). When rejection was accompanied by a significant rise in anti-A/B titers, the patients were treated with plasmapheresis, selective IA columns (Glycosorb®), or both. Antithymocyte globulin and immunoglobulins were given as therapy for rejection in a few cases.

Statistical analysis

The primary endpoints were calculated from the day of LT until September 1, 2012, or to patient death or graft loss. Kaplan–Meier (KM) survival analysis was performed using GRAPH PAD PRISM® version 5 (GraphPad Software, Inc., La Jolla, CA, USA). Survival data were compared using the log-rank test. P values of <0.05 were considered as statistically significant. Overall survival was defined as time from LT to death. GS was defined as time from LT to death or graft failure with retransplantation. Categorical variables were compared using the chi-squared test. The Student's t-test and the Mann–Whitney U-test were used to compare continuous variables between groups.

Results

Patient and graft survival

One-, 3-, 5-, and 10-year KM estimates of total patient survival in the study group were 85%, 79%, 75%, and 59%, respectively, with a median follow-up time was 29 months (range 0–200) (Table 4; Fig. 1a). This result was not significantly different from the corresponding results among all other LTs performed in the same time period, with 1-, 3-, 5-, and 10-year KM estimates of total patient survival of 90%, 84%, 79%, and 65%, respectively. Two acute liver failure patients died of cardiac failure at reperfusion, and two patients died at postoperative days 7 and 8, respectively, one because of multi-organ failure and the other of unknown causes. These four patients accounted for a 30-day mortality of 6.5%. There were no incidents of primary

Table 2. Patient characteristics and results.

Patient	Age/ Sex	ABOi LT was a re-tx	D→R* blood group	Indication for ABOi-tx	Diagnosis	Waiting time (days)	MELD-score	Donor age (years)	PS†	GS‡	Re-tx§
Urgent indications											
1	20/f		A_1→0	ALF/encephalopathy	Budd Chiari	4	40	43	178	0,4	Yes
2	39/f		A_1→0	ALF/encephalopathy	HBV	2	36	22	146	146	
3	33/m		AB→A	ALF	Unknown etiology	1	33	55	94	17	Yes
4	26/f		A_1→0	ALF	Paracetamol intoxication	2	40	38	75	75	
5	24/m		A_1→B	ALF	Paracetamol intoxication	1	40	65	69	69	
6	53/m		A_2→0	ALF	HBV	2	40	27	65	65	
7	51/m		A_1→B	ALF	Digestion of toxic fungus	1	40	59	0	0	
8	67/m		A_1→0	Iatrogenic injury to HA/PV→ALF	Colorectal liver metastasis	3	31	69	23	23	
9	50/m		A_2→0	ALF	Liver trauma/vascular injury	4	30	48	41	41	
10	19/f		A_1→0	ALF	Hemophagocytosis	1	34	31	0,3	0,3	
11	31/f		A_2→0	ALF	Unknown etiology	1	37	64	24	24	
12	31/m		A_1→0	ALF	HBV	3	40	64	22	22	
13	51/m		A_2→0	ALF	HCV/alcoholic cirrhosis	3	40	53	3	3	
14	62/f		A_1→0	AOCLF	PBC	100	40	38	4	4	Yes
15	58/m		A_2→0	AOCLF	Alcoholic cirrhosis	8	21	62	36	36	
16	41/m		A_2→0	AOCLF	Autoimmune hepatitis	23	27	68	0	0	
17	49/m		B→0	AOCLF	HBV/HCV/alcoholic cirrhosis	2	40	43	29	4	Yes
18	52/m		AB→A	AOCLF	Alcoholic cirrhosis	10	40	59	21	21	
19	48/m		A_2→0	AOCLF	Alcoholic cirrhosis	0	38	27	200	200	
20	62/f		B→0	AOCLF	Hemangioandothelioma	17	40	68	2	2	
21	60/f		A_2→0	AOCLF	Autoimmune hepatitis	4	40	40	96	96	
22	35/f		A_2→0	AOCLF	Autoimmune hepatitis	17	26	39	89	89	
23	59/f		A_2→0	AOCLF	PSC	18	31	64	0,3	0,3	
24	43/m		A_2→0	AOCLF	PSC+HCC	30	33	48	72	72	
25	66/f		B→0	AOCLF	PSC	48	32	32	33	33	
26	35/m	Yes	A_2→0	Failure of first graft/AOCLF	Polycystic liver disease	13	38	39	13	13	
27	37/f	Yes	B→0	ALF/rescue-tx, thrombosed graft	Unknown etiology	1	40	44	73	7	Yes
28	20/f	Yes	B→0	Rescue-tx, thrombosed graft	Budd Chiari	1	34	43	54	54	
29	52/f	Yes	A_1→0	Rescue-tx, thrombosed graft	Colorectal liver metastasis	2	14	60	15	15	
30	39/f	Yes	B→0	Rescue-tx due to PNF	Hemangioandothelioma	1	33	66	30	30	
31	56/m	Yes	A_1→0	Rescue-tx due to PNF	PSC	1	18	72	16	16	
32	57/m	Yes	A_2→0	Rescue-tx, thrombosis and infection	Alcoholic cirrhosis	117	27	50	49	49	
33	37/m	Yes	A_2→B	Rescue-tx, PNF	PSC	1	35	40	26	26	
Nonurgent indications											
34	73/f		A_2→0	Cancer / long waiting time	HCV/HCC	97	8	86	61	61	
35	65/m		B→0	Cancer	HCC/varices	11	10	48	12	12	
36	44/f		B→0	Cancer	Colorectal liver metastasis	5	7	41	11	11	
37	64/m		B→0	Cancer	HCV/HCC	114	12	22	6	4	Yes
38	51/f		A_2→0	Cancer	HBV/HCC	70	8	62	94	0,3	Yes
39	53/m		A_2→0	Cancer	HCV/HCC	21	8	46	93	20	
40	51/m		A_2→0	Cancer	HCV/HCC	42	6	53	92	19	
41	58/m		B→0	Cancer / long waiting time	Carcinoid with liver metastasis	187	6	70	27	0,8	Yes
42	46/f		A_2→0	Cancer	HCV/HCC	45	17	66	1,5	1,5	
43	43/m		A_2→0	Cancer / long waiting time	HBV/HCC	174	7	62	38	22	Yes
44	59/m		A_1→0	Cancer / long waiting time	HCV/HCC	353	10	73	7	2	Yes
45	52/m		A_2→0	Cancer / long waiting time	HCV/HCC	282	22	33	25	25	
46	44/m		A_2→0	Cancer / long waiting time	HBV/HCC	645	13	59	20	20	
47	59/f		A_2→0	Long waiting time	PBC/bleeding varices/HCC?	60	20	47	31	18	Yes
48	57/f		A_2→0	Long waiting time	PBC	163	28	58	111	111	

Table 2. continued

Patient	Age/ Sex	ABOi LT was a re-tx	D→R* blood group	Indication for ABOi-tx	Diagnosis	Waiting time (days)	MELD-score	Donor age (years)	PS†	GS‡	Re-tx§
49	46/m		A_2→0	Long waiting time	PSC	696	8	78	24	1,5	Yes
50	59/m		B→0	Long waiting time	PSC	159	10	58	16	1	Yes
51	50/f		A_1→0	Long waiting time	Autoimmune hepatitis	171	12	66	16	16	
52	41/m		B→0	Long waiting time	PSC	525	7	68	10	10	
53	60/f		A_2→0	Encephalopathy/ varices	Alcoholic cirrhosis	37	13	50	71	71	
54	13/m		A_2→0	Encephalopathy	Autoimmune hepatitis	41	18	10	49	49	
55	62/m		A_2→0	Cirrhosis	HBV/alcoholic cirrhosis	60	18	55	121	121	
56	48/m		A_2→0	Cirrhosis	PSC	10	13	52	118	1,5	Yes
57	67/m		A_2→0	Cirrhosis	HCV/alcoholic cirrhosis	38	11	58	77	77	
58	68/m		A_2→0	Cirrhosis	HCV	60	9	57	76	76	
59	66/m		A_2→0	Cirrhosis	Alcoholic cirrhosis	126	29	59	70	70	
60	57/m		B→A	Cirrhosis	HCV	86	21	57	36	36	
61	75/m		AB→B	Cirrhosis	Alcoholic cirrhosis	49	12	73	17	17	

ALF; acute liver failure; HBV; hepatitis B virus, HCV; hepatitis C virus, AOCLF; acute on chronic liver failure, HCC; hepatocellular carcinoma, PBC; primary biliary cirrhosis; PSC; primary sclerosing cholangitis, PNF; primary nonfunction, HA; hepatic artery, PV; portal vein.
*Donor → recipient.
†Patient survival (months).
‡Graft survival (months).
§Retransplantation due to failure of ABOi graft.

Table 3. Immunosuppression.

Donor→recipient blood group	A_1→0	A_1→B	A_2→0	A_2→B	AB→A	AB→B	B→0	B→A	$ABOi_{total}$
Number of patients	11	2	31	1	2	1	12	1	61
Immunosuppression									
Standard*	8 (72.7%)	2 (100%)	20 (64.5%)	1 (100%)	2 (100%)	1 (100%)	9 (75%)	1 (100%)	44 (72.1%)
Steroids/TAC†		7 (22.6%)				1 (8.3%		8 (13.1%)	
MMF‡/TAC			3 (9.7%)				1 (8.3%		4 (6.6%)
Other	3 (27.3%)		1 (3.2%)				1 (8.3%		5 (8.2%)
Anti IL2§	7 (63.6%)	1 (50%)	16 (51.6%)	1 (100%)	1 (50%)	1 (100%)	7 (58.3%)	1 (100%)	35 (57.4%)
Anti CD20¶	9 (81.8%)	1 (50%)	7 (22.6%)	1 (100%)	1 (50%)	1 (100%)	9 (75%)	1 (100%)	30 (49,2%)
ATG**	1 (9.1%)		2 (6.5%)				3 (25%)		6 (9.8%)
Immunoglobulin	7 (63.6%)		9 (29.0%)	1 (100%)	2 (100%)	1 (100%)	7 (58.3%)	1 (100%)	28 (45.9%)

*Steroids, tacrolimus and mycophenolate mofetil.
†Tacrolimus.
‡Mycophenolate mofetil.
§Anti-interleukin-2 (basiliximab or daclizumab).
¶Rituximab.
**Antithymocyte globulin.

nonfunction among the ABOi livers. One-, 3-, 5-, and 10-year KM estimates of total GS were 71%, 57%, 55%, and 51%, compared to 87%, 79%, 73%, and 60%, respectively, in the NLTR group ($P = 0.0003$) (Table 4; Fig. 1b). In a subgroup analysis of patients receiving A_2 grafts, the 1-, 3-, 5-, and 10-year GS were 81%, 67%, 62%, and 57%, respectively (Table 5; Fig. 2). These results were in line with those in the NLTR group ($P = 0.14$). The corresponding comparison for the non-A_2 group compared to the NLTR group clearly showed inferior GS in the non-A_2 group ($P < 0.0001$) (Fig. 2). When comparing GS in the A_2 group versus the non-A_2 group, the difference was not statistically significant ($P = 0.16$), possibly because of the limited number of patients in each group. However, it appeared that the non-A_2 group had inferior GS compared to the A_2 group (Table 5 and Fig. 2). In the subgroup analysis of patients transplanted because of urgent indications ($n = 33$), the 1-, 3-, 5-, and 10-year GS values were 74%,

Table 4. Results.

	$ABOi_{total}$	NLTR* 1996–2011	*P*-value	HR	CI
Acute rejection†	28 (45.9%)				
AMR‡	4 (6.5%)				
CIT§ (minutes)¶	435 (249–1050)				
Retransplantation rate	14 (23%)				
Patient survival (KM)**					
1 year	85%	90%	0.27	1.38	0.78–2.44
3 year	79%	84%			
5 year	75%	79%			
10 year	59%	65%			
Graft survival (KM)**					
1 year	71%	87%	0.0003	2.77	1.60–4.81
3 year	57%	79%			
5 year	55%	73%			
10 year	51%	60%			
Complications					
Vascular	16 (26.2%)††				
Biliary	17 (27.9%)				

*Nordic Liver Transplant Registry.
†Biopsy proven and/or clinical signs of rejection.
‡Antibody-mediated rejection.
§Cold ishemic time.
¶Median and range.
**Kaplan–Meier estimate.
††14.8% (n = 9) hepatic artery thrombosis or stenosis/stricture.

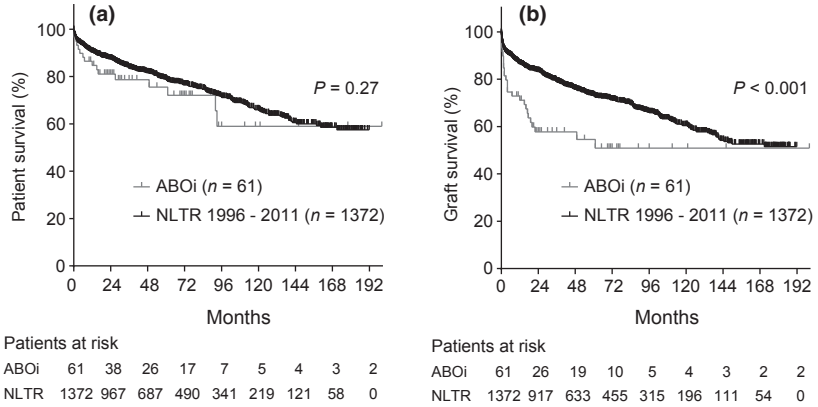

Figure 1 Kaplan–Meier plots of (a) patient and (b) graft survival in the total ABO-incompatible group versus ABO-compatible liver transplantations in the Nordic Liver Transplant Registry transplanted in the period 1996–2011.

64%, 58%, and 58%, respectively. The corresponding results for the nonurgent group (n = 28) were 68%, 49%, 49%, and 42%, respectively (P = 0.37) (Fig. 3).

Retransplantations

The rate of retransplantations in the total study population was 23% (14 patients). This rate in the A_2 group was 16% (5/32) vs. 31% (9/29) in the non-A_2 group (P = 0.15) (Table 5). Of these 14 patients, seven patients were retransplanted because of biliary complications as the major cause, three patients because of vascular problems, three patients for acute rejection, and one patient because of relapse of hepatitis C virus (HCV). Ten of these retransplantations (71%) occurred within the first 4 months after the primary transplantation.

Vascular complications

In total, 16 patients (26%) were diagnosed with vascular complications during the follow-up period (Table 4). Nine

Table 5. Patient characteristics and results A_2 versus A_1,B,AB.

	ABOi-A_2	ABOi-A_1,B,AB	*P*-value	RR/HR*	CI
Number of patients	32	29			
Patient age (years)†	51 (13–73)	51 (19–75)	0.59‡		
Donor age (years)†	53 (10–86)	58 (22–73)	0.71§		−9.36 to 6.42
MELD score†	21 (6–40)	33 (6–40)	0.14‡		
Acute rejection¶	37.5%	55.2%	0.17**	0.71	0.42 to 1.17
AMR††	3.1%	10.3%	0.26**	0.46	0.08 to 2.55
CIT¶ (minutes)†	456 (273–1050)	420 (249–738)	0.051‡		−0.55 to 174.7
Retransplantation rate	5 (15.6%)	9 (31.0%)	0.15**	0.62	0.29 to 1.31
Patient survival (KM)‡‡					
1 year	90.3%	78.2%	0.25	0.56*	0.21 to 1.52
3 year	83.6%	64.5%			
5 year	78.4%	64.5%			
10 year	72.8%	64.5%			
Graft survival (KM)‡‡					
1 year	80.6%	60.3%	0.16	0.56*	0.25 to 1.26
3 year	67.0%	47.9%			
5 year	62.2%	47.9%			
10 year	57.1%	47.9%			
Complications					
Vascular	6 (18.8%)	10 (34.5%)	0.16**	0.65	0.33 to 1.28
Biliary	7 (21.9%)	10 (34.5%)	0.27**	0.72	0.39 to 1.35

CI, 95% confidence interval; RR, relative risk; HR, hazard ratio.
*Hazard ratio.
†Median and range.
‡Mann–Whitney *U*-test.
§Student's *t*-test.
¶Biopsy proven and/or clinical signs of rejection.
**Chi-squared test.
††Antibody-mediated rejection.
‡‡Kaplan–Meier estimate.

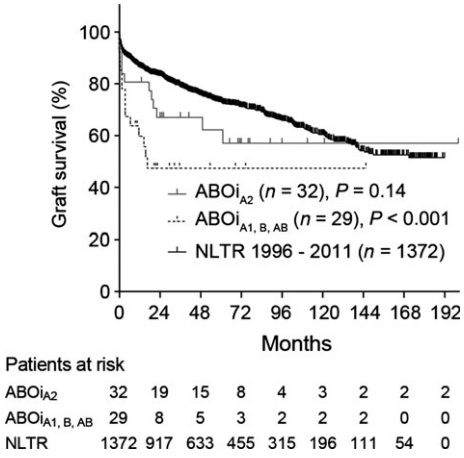

Figure 2 Kaplan–Meier plot of graft survival in the A_2 subgroup and non-A_2 subgroup of ABO-incompatible liver transplantations versus ABO-compatible transplantations in the Nordic Liver Transplant Registry transplanted in the period 1996–2011.

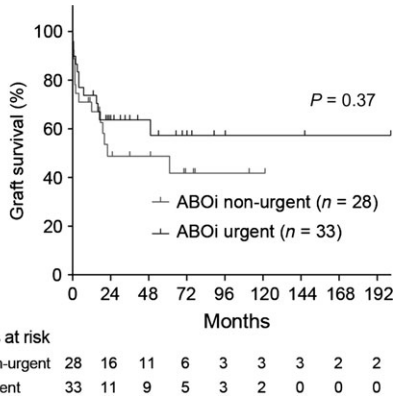

Figure 3 Kaplan–Meier plot comparing graft survival among ABO-incompatible patients transplanted for urgent versus nonurgent indications.

patients (15%) had hepatic artery thrombosis or stenosis/stricture that affected the hepatic artery. Of these 16 incidents, 11 (69%) occurred within 30 days from LT. Six patients (10%) were diagnosed with thrombosis of the portal vein, of whom one patient also suffered from a ruptured hepatic artery. One patient was found to have a mycotic pseudo-aneurysm on the hepatic artery (bacterial culture showed enterococci of undetermined subtype).

Of these 16 patients, five required retransplantation as primary treatment, seven were managed by early reoperation, and one patient with portal vein thrombosis was treated with intensive anticoagulation. Two patients with a relative stenosis of the hepatic artery and one patient with thrombus in the portal vein did not need any active treatment. Of the 14 patients in the study who required retransplantation, nine were diagnosed with some form of vascular complication. The rate of vascular complications was 19% in the A_2 subgroup and 34.5% in the non-A_2 group ($P = 0.16$) (Table 5).

Biliary complications

A total of 17 patients (28%) presented with some sort of biliary complications after the LT (Table 4). Of these 17 patients (59%), 10 were also diagnosed with vascular complications, of which 70% were arterial. Seven of these seventeen incidents (41%) occurred within 30 days from LT. Eight patients were diagnosed with biliary leakage, four with stenosis, and one patient with both. Three patients developed necrosis of the common bile duct without evidence of leakage, and two patients had multiple episodes of cholangitis accompanied by radiological signs of strictures affecting intrahepatic biliary ducts. Two of these patients required retransplantation as primary treatment, and six patients were managed by reoperation with suture of leakage or new biliary anastomosis. Seven patients were successfully treated by endoscopic retrograde cholangiography with blocking alone or together with temporary stenting, and one patient was managed by percutaneous transhepatic cholangiography with a temporary stent. One patient with a relative discrete biliary stenosis did not need any active treatment. Overall, 10 of the 17 patients (59%) were diagnosed with biliary complications that eventually required retransplantation. However, only seven of the retransplantations had biliary problems as the main cause. The rates of biliary complications in the A_2 group versus the non-A_2 group were 22% and 35%, respectively ($P = 0.27$).

Rejections

Of the 61 patients, 28 (46%) were treated for acute rejections, defined as rejection within the first 4 weeks postoperatively (Table 6). The biopsy-proven rejection rate was 39% ($n = 24$), and 14% ($n = 4$) had rejections based only on clinical suspicion ($n = 4$, 14%). Three patients had biopsy-proven humoral rejection ($A_1 \rightarrow 0$, $A_2 \rightarrow 0$, and $B \rightarrow 0$), and one patient ($B \rightarrow 0$) was regarded as having AMR based on clinical suspicion. The A_2 donor–recipient with AMR had a pretransplant positive cross-match. Figure panels 4a and b illustrate typical findings in one of the patients with biopsy-proven AMR. Thus, the total rate of AMR was 6.5%, and the overall rejection rate was 37.5% ($n = 12/32$) in the A_2 group and 55% ($n = 16/29$) in the non-A_2 group ($P = 0.17$).

Only 27 of the 61 patients received PP ($n = 18$) and/or IA column absorption ($n = 19$) treatment after LT. Eight patients received both types of treatment.

Rejection and antibody titers

Anti-A and anti-B antibody titers were measured regularly during the first 4 weeks in most patients. Despite a potential correlation in our data between an increase in anti-A and/or B antibody titer post-LT and the occurrence of ACR/AMR rejection, the data are limited, precluding a definitive conclusion. However, ABOi LT in the presence of anti-HLA donor-specific antibodies (DSAs) at the time of LT ($n = 8$) seemed to result in inferior GS (Fig. 5, $P = 0.058$). Further details are given in Table 7.

Table 6. Rejection and treatment.

Donor→recipient blood group	$A_1 \rightarrow 0$	$A_1 \rightarrow B$	$A_2 \rightarrow 0$	$A_2 \rightarrow B$	$AB \rightarrow A$	$AB \rightarrow B$	$B \rightarrow 0$	$B \rightarrow A$	$ABOi_{total}$
Number of patients	11	2	31	1	2	1	12	1	61
Acute rejection	7 (63.6%)	1 (50%)	12 (38.7%)		2 (100%)		6 (50%)		28 (45.9%)
AMR*	1 (9.1%)		1 (3.2%)				2 (16.7%)		4 (6.5%)
Plasmapheresis (PP)	5 (45.5%)		8 (25.8%)	1 (100%)	2 (100%)		2 (16.7%)		18 (29.5%)
Glycosorb columns (GSC)	8 (72.8%)	1 (50%)	3 (9.7%)	1 (100%)	1 (50%)	1 (100%)	3 (25%)	1 (100%)	19 (31.1%)
Both PP and GSc	3 (27.3%)		2 (6.5%)	1 (100%)	1 (50%)		1 (8.3%)		8 (13.1%)
ATG†	1 (9.1%)		1 (3.2%)						2 (3.3%)
Immunoglobulines							1 (8.3%)		1 (1.6%)
OKT-3‡	1 (9.1%)								1 (1.6%)

*Antibody-mediated rejection.
†Antithymocyte globulin.
‡Muromonab-CD3.

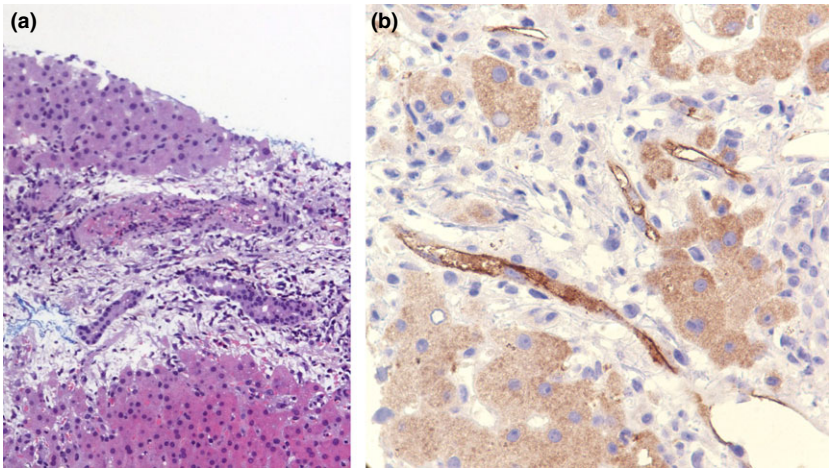

Figure 4 Typical histopathological picture in a patient with antibody-mediated rejection showing (a) portal edema, inflammatory infiltration, and necrosis of the portal artery wall and (b) C4d staining of portal capillaries.

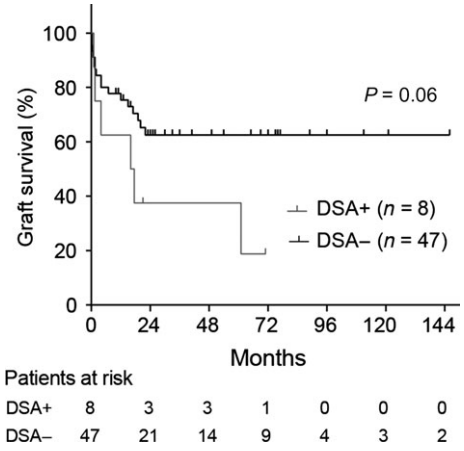

Figure 5 Kaplan–Meier plot comparing graft survival in the donor-specific antibody (DSA)-positive subgroup versus the DSA-negative subgroup.

Discussion

In most countries, liver grafts are a scarce resource, leading to a significant death rate for patients on the LT waiting lists. ABOi LT may be an option for providing liver grafts for patients in urgent need of transplantation who would otherwise not be transplanted and may also become a viable option available for nonurgent and elective cases if the results can be improved to the level obtained from ABOc LT.

This study was an uncontrolled retrospective observational study; however, it represents one of the largest patient cohorts of deceased donor LTs using A_2 and non-A_2 ABOi grafts for both urgent and nonurgent indications. In 2009, Stewart *et al.* [7] published data on ABOi from the UNOS database with 667 adult patients, but without discriminative analysis performed between A_1 and A_2 grafts. Other studies have reported variable results from mostly smaller patient cohorts and with relatively short follow-up [2,3,6]. The majority of these studies have not distinguished between A_1 and A_2 grafts. Toso *et al.* [9] reported a 5-year GS of 56% in a group of 14 ABOi patients with acute liver failure, and the results did not differ significantly from the corresponding results achieved among ABOc LT recipients. Urbani *et al.* reported 18-month GS of 58% in 19 ABOi patients. The GS was improved with an 18-month GS of 88% in a subgroup of eight patients who were treated with therapeutic plasma exchange in combination with extracorporal photopheresis and high-dose immunoglobulins [23]. In a study from 1995, Farges *et al.* [11] published results from 43 ABOi LTs with a 5-year GS of 20%. Notably, these patients were transplanted between 1986 and 1992, which involved surgical techniques and immunosuppressive medications that are not in current use.

Elective living donor ABOi LTs are currently being performed with excellent results at transplant centers in Asia, with patient survival close to what is achieved in ABOc LT [16,19,21,22]. Induction with anti-CD20 antibody (rituximab) and preoperative PP is incorporated into most of the immunosuppressive protocols [20]. The indications for LT in Asian countries differ from those of the Northern European and Scandinavian patient populations, with a higher frequency of hepatocellular carcinoma (32% vs. 19%) [22]. The age distribution in Japan also has a significantly higher number of young patients than in Scandinavia, with 36% of patients under age 18 years at the time of transplantation versus 8% under age 16 years and 14% under age 30 years in Scandinavia. In our study, only one of 61 patients was under age 18 years at the time of transplantation.

Table 7. Rejection, DSA, and anti-ABO antibody titers.

Patient	Donor→recipient blood group	Acute rejection	AMR*	Anti-HLA DSA	IgM_0†	IgG_0†	IgM_{max}‡	IgG_{max}‡	Titer-steps IgM§	Titer-steps IgG§	Re-tx¶
1	A_1→0	Yes			512	512	512	512	0	0	Yes
2	A_1→0	Yes			1	4	32	256	5	6	
3	AB→A	Yes			4	16	32	128	3	3	Yes
4	A_1→0	Yes			0	2	32	256	6	7	
5	A_1→B	Yes			2	4	8	32	2	3	
6	A_2→0				8	32	16	128	1	2	
7	A_1→B										
8	A_1→0				16	32	256	256	4	3	
9	A_2→0				32	256	32	256	0	0	
10	A_1→0				4	16	1	8	<0	<0	
11	A_2→0	Yes			4	8	256	512	6	6	
12	A_1→0	Yes			4	16	1	4	<0	<0	
13	A_2→0	Yes		na	32	256	64	256	1	0	
14	A_1→0	Yes	Yes	Yes	1	8	1024	4096	10	9	Yes
15	A_2→0				8	64	128	512	4	3	
16	A_2→0										
17	B→0	Yes			1	8	1	8	0	0	Yes
18	AB→A	Yes		Yes	2	4	32	32	4	3	
19	A_2→0	Yes		na	64	1024	1024	1024	4	0	
20	B→0	Yes		na	16	256	16	256	0	0	
21	A_2→0				128	512	128	512	0	0	
22	A_2→0	Yes			64	128	512	2048	3	4	
23	A_2→0	Yes		na	128	1024	4	64	<0	<0	
24	A_2→0				32	64	4	16	<0	<0	
25	B→0				16	32	0	2	<0	<0	
26	A_2→0				32	128	2	16	<0	<0	
27	B→0				2	32	8	32	2	0	Yes
28	B→0	Yes			1	1	8	8	3	3	
29	A_1→0	Yes			1	8	1	8	0	0	
30	B→0				16	1	16	2	0	1	
31	A_1→0	Yes		Yes	4	1	32	32	3	5	
32	A_2→0	Yes		na	1	32	2048	32 768	11	10	
33	A_2→B				2	2	128	128	6	6	
34	A_2→0	Yes		Yes	32	1024	32	1024	0	0	
35	B→0	Yes	Yes		1	2	128	32	7	4	
36	B→0	Yes			2	4	2	8	0	2	
37	B→0				16	128	128	2048	3	4	Yes
38	A_2→0				64	1024	4096	8192	6	3	Yes
39	A_2→0	Yes			16	256	128	1024	3	3	
40	A_2→0						64	256			
41	B→0	Yes	Yes		32	1024	1024	4096	4	2	Yes
42	A_2→0	Yes	Yes	Yes	32	32	64	64	1	1	
43	A_2→0				64	512	64	512	0	0	Yes
44	A_1→0				16	64	4	8	<0	<0	Yes
45	A_2→0						32	32			
46	A_2→0	Yes			32	64	32	64	0	0	
47	A_2→0	Yes		Yes	16	128	256	2048	4	4	Yes
48	A_2→0						1024	8192			
49	A_2→0				32	256	128	1024	2	2	Yes
50	B→0			Yes	4	16	4	16	0	0	Yes
51	A_1→0				4	8	0	2	<0	<0	
52	B→0				8	16	8	8	0	<0	
53	A_2→0			Yes	32	256	32	256	0	0	
54	A_2→0	Yes			32	64	32	64	0	0	
55	A_2→0				64	512	512	1024	3	2	

Table 7. continued

Patient	Donor→recipient blood group	Acute rejection	AMR*	Anti-HLA DSA	IgM_0†	IgG_0†	IgM_{max}‡	IgG_{max}‡	Titer-steps IgM§	Titer-steps IgG§	Re-tx¶
56	A_2→0				16	512	512	8192	5	4	Yes
57	A_2→0						128	1024			
58	A_2→0				128	512	8	64	<0	<0	
59	A_2→0	Yes		na	1	2	2	8	1	2	
60	B→A				0	2	1	4	1	1	
61	AB→B				0	2	0	2	0	0	

*Antibody-mediated rejection.
†Titer levels at the time of transplantation.
‡Maximum titer levels.
§For example, titers rising from 8 to 32 means 2 steps.
¶Retransplantation due to failure of the ABOi graft, na; data on DSA not available.

Furthermore, the clinical conditions of the patients in non-elective transplantations are often more severe, and there is no or limited time available for preconditioning treatment. These factors may in combination contribute to the superior graft and patient survival that is observed in elective living donor ABOi LT [22].

Recent findings demonstrate that DSAs or de novo DSAs after ABOc LT are associated with inferior graft and patient survival [24–28]. This outcome may indicate that the presence of antibody-driven rejection *per se* is the determining factor and not whether the antibody specificities are toward HLA or ABO antigens. Our patient cohort is too small to determine the impact and relative importance of antibody specificities, but our data indicate that the combination of DSA and ABOi is associated with inferior GS. Close follow-up with immunologic and biochemical evaluations should be considered, and immunosuppressive medication may need to be intensified and adjusted accordingly. Our findings also indicate a possible association between an increase in anti-ABO titer and rejection. However, the levels of ABO antibodies in peripheral blood are influenced by previous infections, the individual propensity of T- and B-cell-driven immunoreactivity, and the degree of graft absorption [29]. Thus, it is not clear whether an increase in anti-ABO titers is useful for clinical decision-making regarding antibody-eradicating treatment. However, in a recently published study by Shen *et al.* [30], only the patients who experienced a rise in anti-ABO titers following ABOi LT developed biopsy-proven AMR, which supports the notion that efforts should be undertaken to reduce ABO titers post-ABOi LT.

We experienced that the complications in our patient cohort were frequently arterial and bile duct strictures and thrombosis. In total, 26% of the patients experienced vascular complications with hepatic artery thrombosis as the dominating cause. In a systematic meta-analysis on early hepatic artery thrombosis after LT, the incidence was 3% in adults [31]. Berstad *et al.* [32] reported a total incidence of hepatic artery thrombosis of 3% in a series of 152 ABOc LTs, and portal vein complications (thrombosis and stenosis) have been reported to occur in 1–2% of LT patients [33]. A vascular component may have been a contributing factor to or leading cause of the biliary complications experienced in our patient cohort because the bile ducts receive their blood supply from the hepatic artery [34–36]. The biliary complications were the most common cause of retransplantations; however, most of the complications could be managed surgically or endoscopically without the need for a new graft.

Recipients of A_2 liver grafts appeared to have fewer vascular and biliary complications. The difference between A_2 liver grafts and other ABOi grafts with respect to graft and patient survival, acute rejections, and the rate of retransplantations also favoured A_2 LT. This may be due to a lower expression of blood group A antigen in A_2 grafts as has been demonstrated in kidneys [37]. This is in line with previous reports [12,15] and supports that A_2 ABOi liver graft can be safely used in critical situations. On the other hand, it is likely that the prognosis and rate of complications of other non-A_2 ABOi LTs can be improved with optimization of immunosuppressive regimens, desensitization strategies, and better understanding of rejection reactions.

One limitation of this study is that the transplants were performed over an extended time period, at two transplant centers in two different counties, and with a very heterogeneous immunosuppressive approach. Most of the patients were not treated according to what we today would consider adequate pre-ABOi LT conditioning and immunosuppression. Available data from living donor ABOi kidney transplantation and the Asian experience with ABOi living donor LT support the need for anti-ABO antibody and B-cell depletion, anti-ABO antibody monitoring in addition to maintain immunosuppression [38]. This may explain

the inferior outcome in our study in the non-A_2 group. Recently, Shen *et al.* have published promising results from China on 35 acute liver failure patients who underwent LT with deceased donor ABOi grafts. The patients were treated with anti-CD20 antibody (rituximab) and IVIG (0.4 g/kg/day) prior to the transplant and triple immunosuppression and plasma exchange was performed only if needed postoperatively. Graft and patient survival did not differ significantly from that of patients receiving ABOc grafts [30]. Based on our current experience and the available knowledge in the literature, we have now implemented an ABOi LT protocol for high urgent liver failure involving pre- and post-LT ABO antibody depletion, B-cell depletion, triple immunosuppression, and an intensified thrombosis prophylaxis post-LT. Another consideration of this study is that the epidemiology and disease panorama represents that of the Scandinavian population. The prevalence of HCV in Scandinavia is lower than in many South European countries and in particular compared to the prevalence found in South-East Asia. In addition, the prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis is also substantially lower in Scandinavia than in the USA.

Regarding the ethical considerations when performing ABOi LT within the Scandia Transplant Network the following consideration have been made; The criteria for listing patients on high urgent call within Scandia Transplant are well defined and excludes acute on chronic patients and patients beyond 14 days after their previous LT. Although the liver availability within Scandia Transplant is better than in many other countries in Europe and around the world, acutely ill patients in the ICU still run a substantial risk of dying if they have to wait for an ABOc liver graft. Importantly, we always prioritize to wait for an ABOc graft if time allows. The mortality on the waiting list in Sweden and Norway is very low especially in blood group A, B, and AB (<5%). When an ABOi LT is being considered, it is always carried out with the consideration of the other patients on the waiting list. Both centers are very reluctant to use an ABO-incompatible graft if this would jeopardize the life of an ABO-compatible recipient. With the organ availability in Scandia Transplant and the low waiting list mortality, Scandia Transplant members find this practise ethically acceptable.

In conclusion, this study illustrates that ABOi LT performed with non-A_2 grafts is associated with inferior graft survival and increased risk of rejection, vascular and biliary complications. ABOi LT performed with A_2 grafts is associated with good long-term graft survival and can be used safely in urgent cases. However, future studies are needed to evaluate if ABO antibody- and B-cell depletion protocols can improve the outcome following non-A_2 ABOi LT using deceased donors.

Authorship

TT, USD, AF, and WB: designed the study, analyzed data, and wrote the paper. EM, KG, THK, KMB, LR, and CN: analyzed data and wrote the paper. TT, USD, KG, LR, and CN: collected data.

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