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ORIGINAL ARTICLE

Single cohort study: ABO-incompatible kidney transplant recipients have a higher risk of lymphocele formation

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Abstract

Purpose Since 2004, ABO-incompatible kidney transplantation (ABOi KTx) became an established procedure to expand the living donor pool in Germany. Currently, ABOi KTx comprises > 20% of all living donor KTx. Up to September 2015, > 100 ABOi KTx were performed in Freiburg. Regarding lymphocele formation, only scarce data exist.

Methods Between April 2004 and September 2015, 106 consecutive ABOi and 277 consecutive ABO-compatible kidney transplantations (ABOc KTx) were performed. Two ABOi and 117 ABOc recipients were excluded due to differences in immunosuppression. One hundred-four ABOi and 160 ABOc KTx patients were analyzed concerning lymphocele formation.

Results The incidence of lymphoceles in ABOi KTx was 25.2% and 10.6% in ABOc KTx ($p = 0.003$). A major risk factor appeared the frequency of ≥ 8 preoperative immunoadsorption and/or plasmapheresis sessions (OR 5.61, 95% CI 2.31–13.61, $p < 0.001$). Particularly, these ABOi KTx recipients had a distinctly higher risk of developing lymphocele (40.0% vs. 19.2%, $p = 0.044$). IA/PE sessions on day of transplantation (no lymphocele 20.0% vs. lymphocele 28.6%, $p = 0.362$) or postoperative IA/PE sessions (no lymphocele 25.7% vs. lymphocele 24.1%, $p = 1.0$) showed no influence on formation of lymphoceles.

Conclusion In ABOi KTx, the incidence of lymphocele formation is significantly increased compared to ABOc KTx and leads to more frequent surgical reinterventions without having an impact on graft survival.

Keywords ABO-incompatible kidney transplantation · Renal transplantation · Blood group-incompatibility · Immunoadsorption · Surgical complications

Introduction

In April 2004, ABO-incompatible kidney transplantation was introduced in Germany. Since then, over 100 ABOi KTx were performed at our institution, comprising > 20% of all living donor kidney transplantations per year. Initial concerns about long-term graft and patient survival of ABOi KTx were resolved, and posttransplantation outcome is now comparable to ABO-compatible kidney transplantation [1–4]. These excellent long-term results are based on an improved immunosuppression protocol [1, 2, 5]. This protocol was developed according to a Swedish protocol established in 2001 [6]. For ABOi KTx recipients, our protocol comprises an anti-CD20 treatment with rituximab (375 mg/m^2) and repetitive immunoadsorption before transplantation. In addition, the immunosuppressive maintenance therapy is started 1 week prior to the transplantation [1, 2].

This study analyzes postoperative lymphocele formation of all patients since 2004 transplanted in our ABOi KTx program receiving basiliximab induction and immunosuppressive maintenance therapy including a calcineurin inhibitor, mycophenolate acid, and steroids. Our control study group consisted of our ABOc KTx program transplanted within the same time period and treated with an as similar as possible

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immunosuppressive protocol (basiliximab induction and immunosuppressive triple therapy consisting of a calcineurin inhibitor, mycophenolate acid, and steroids).

Despite the more intensive immunosuppressive therapy, the incidences of infections and malignancies were not increased [1, 2, 5]. However, a higher risk of postoperative bleeding, leading to a significantly increased rate of red blood cell transfusions, was repeatedly reported [7–11]. So far, data on additional surgical complications, especially with the focus on the development of lymphoceles, in the context of ABOi KTx are scarce, occasionally contradictory and generally based on a rather limited number of cases [12–14].

Based on our clinical experience, we assumed a negative impact of ABOi KTx on lymphocele formation. The aim of this study is to substantiate this suspicion and identify possible risk factors.

Materials and methods

Endpoint and study design

This study examined the incidence of lymphocele formation after ABO-compatible and ABO-incompatible living donor kidney transplantation between April 2004 and September 2015 at the Freiburg Transplant Center. The data were extracted from our [prospectively conducted] living donor kidney transplant registry. During this time period, a total of 383 living donor kidney transplantations (106 ABOi and 277 ABOc KTx) were performed. All recipients who received basiliximab induction (Simulect®, Novartis AG, Basel, Switzerland) and a calcineurin-inhibitor- (tacrolimus (Prograf®, Astellas Seiyaku K.K., Tokio, Japan) or cyclosporine (Sandimmun Optoral®, Novartis AG, Basel, Switzerland)), mycophenolic acid- (CellCept®, Roche Pharma AG, Grenzach-Wyhlen, Germany) and prednisone-based immunosuppressive triple maintenance therapy were included in the study. In 119 cases (2 ABOi and 117 ABOc KTx) we deviated from our current standard immunosuppressive protocol: Twenty-five recipients (2 ABOi and 23 ABOc KTx) were kept on a different immunosuppressive regimen due to various medical issues such as drug incompatibility or immunization and 94 ABOc KTx patients with a low immunological risk profile (1st degree relationship to donor, no panel reactive antibodies (PRAs), ≤ 3 HLA-mismatches) received no immunosuppressive induction therapy. These patients were excluded from the present analysis. Finally, 104 ABOi and 160 ABOc KTx patients met all inclusion criteria (Fig. 1). One ABOi KTX recipient died during the first night after transplantation due to severe myocardial infarction and was omitted from this study.

Donor assessment, donor nephrectomy, and graft preparation

Before living donation, the medical suitability of the donors was accurately screened in a 3-day inpatient examination. Subsequently, for medically suitable donors, the required statutory approval by the transplantation ethics committee of the District Medical Association Südbaden was obtained. The donor nephrectomy was performed in supine position over a minimal-incision extraperitoneal open anterior access. Since March 2015, a laparoscopic transperitoneal hand-assisted approach was preferred for donor nephrectomy. Immediately after retrieval, the procured kidney was cooled and flushed with cold heparin solution (5000 units in 150 ml of saline), followed by 1 l of histidine-tryptophan-ketoglutarate solution (Custodiol®, Dr. Franz Köhler Chemie GmbH, Bensheim, Germany). Of note according to our initial protocol, the first 26 kidneys of our ABOi KTx program were flushed with 20,000 units of heparin dissolved in 50 ml of saline. Subsequently, the prepared kidney was stored on ice at 6 °C until implantation in the recipient.

Surgical procedure and recipient follow-up

The implantation was scheduled in the same operating theater directly after the donor nephrectomy to keep the cold ischemic time as short as possible. The kidney transplantation was performed in the established technique usually to the right iliac fossa of the recipient. The lymphatic tissue covering the blood vessels was removed thoroughly, keeping the vascular implantation sites as small as possible, and subsequently ligated. All surgical procedures were performed by an experienced surgical team involving a total 5 surgeons. Until postoperative day 5, all recipients received a fixed dose of 12,500 units of heparin intravenously per day, starting 6 h after the end of surgery. DJ catheters were routinely removed after 10–15 days. All recipients were treated for approximately 2 weeks on our transplant ward. During inpatient care, ultrasound was performed twice a week in asymptomatic recipients or in case of local medical condition. After hospital discharge, regular follow-up examinations (including ultrasound) took place in our nephrologic transplant outpatient clinic at 1, 2, 3, 6, and 12 months after discharge. In between the recipients were regularly seen by their local nephrologist.

ABO-incompatible KTx protocol

All ABOi recipients received a single dose of rituximab (375 mg/m^2 body surface, MabThera®, Roche Pharma AG, Grenzach-Wyhlen, Germany) approximately 4 weeks before scheduled kidney transplantation. Seven days prior to surgery, the triple maintenance therapy, including tacrolimus (trough levels 12–15 ng/ml), 2 g of mycophenolate acid daily and 30 mg of

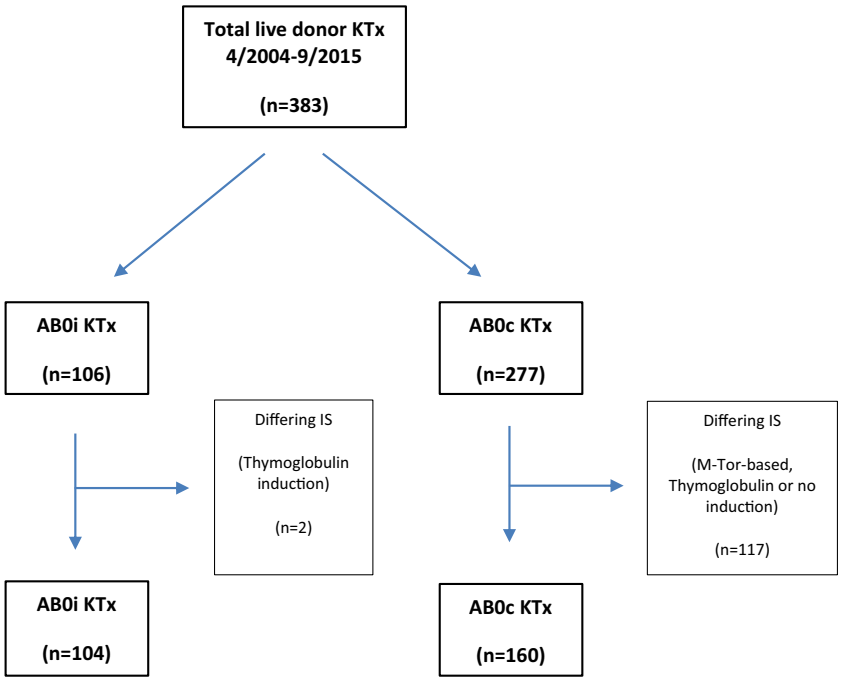

Fig. 1 Study profile: the study comprises all recipients of the Freiburg Transplant Center, receiving a live donor kidney transplant and an immunosuppressive therapy consisting of basiliximab, calcineurin inhibitor, mycophenolate acid and steroids. ABOi ABO-incompatible, ABOc ABO-compatible, KTx kidney transplantation, IS immunosuppression

prednisone per day was started. Antibody elimination (immunoadsorption/plasmapheresis) was initiated 1 week prior to scheduled surgery. For immunoadsorption, a commercially available apheresis device (Octo Nova™, Diamed Medizintechnik, Cologne, Germany), hollow-fiber plasma separators (P2™, Fresenius Medical Care, Bad Homburg, Germany or Microplas MPS 07™, Bello, Italy) and until November 2012 antigen-specific adsorption columns (Glycosorb A/B™, Glycorex, Lund, Sweden) and since December 2012, reusable non-specific immunoglobulin adsorption columns (Immunosorba™, Fresenius Medical Care, Bad Homburg, Germany) were utilized. Immunoadsorption was performed as described before [5]. Target isohaemagglutinine titers were ≤ 1:4 on the day of surgery, ≤ 1:8 from postoperative day 1–7, and ≤ 1:16 until postoperative day 14 for IgG and IgM titers. If the target titers were not reached solely by non-specific immunoadsorption, additional plasma exchanges were executed. The amount of fresh frozen plasma (FFP) was individually calculated, solely using 100% blood type AB FFP ≤ 2 before transplantation. During the first postoperative week, isohaemagglutinine titers were monitored in daily intervals and during week 2 every second day. In case of exceeded postoperative threshold values, immunoadsorption was performed immediately on demand, until reaching the abovementioned target levels. All ABOi KTx recipients received induction therapy with basiliximab (20 mg on days 0 and 4). Intraoperatively 500 mg of prednisone was administered before reperfusion. Prednisone was tapered with 250 mg on day 1, 125 mg on day 2 until 15 mg at discharge on day 14. Tacrolimus trough levels were regulated between 8 and 12 ng/ml until postoperative day 7, and then decreased to 8–10 ng/ml during the next 5 weeks. Mycophenolate mofetil was applied twice daily (2 g per day).

Current immunosuppressive protocol for ABO-compatible KTx recipients

All ABOc KTx recipients received induction with basiliximab (20 mg intraoperatively and on day 4, respectively). Prednisone was administered starting with 250 mg intraoperatively, 125 mg on the 1st postoperative day, 50 mg on postoperative day 2, and then quickly tapered to 15 mg on day 12. Tacrolimus trough levels were targeted at 8–10 ng/ml and mycophenolate acid (fix dose of 2 g daily) initiated at the evening prior to transplantation.

Clinical data collection, definitions, and statistical analysis

Clinical data were continuously collected from direct patient care and clinical records. Follow-up data were collected from the responsible nephrologists throughout Germany. Supplemental surgical interventions were simultaneously performed if necessary and comprised appendectomy and nephrectomy, including ipsilateral polycystic and natural kidneys for space reasons, and former failed kidney grafts for immunological reasons. Delayed graft function was defined by the need of at least one dialysis treatment during the first postoperative week. Lymphocele formation was defined as newly occurring perirenal fluid collection of more than

100 ml during the first 3 months after transplantation determined by ultrasound examination after removal of wound drainage. Usually, the wound drainage was removed between days 5 and 10, once secretion was less than 100 ml per day. In all cases, urinoma and hematoma were excluded by diagnostic puncture. Lymphoceles were categorized according to conservative or surgical treatment.

If possible, data are expressed as a mean ± standard deviation. The group comparison (including sub-group analysis for ABOi KTX recipients) for categorical data was performed with 2-tailed Fisher's exact test and the one for continuous data with Mann-Whitney *U* test (GraphPad Prism 8). Multivariate analysis was performed and Kaplan-Meier survival graphs were prepared with MedCalc® V 19.0 (MedCalc Software, www.medcalc.org). All striking parameters of the univariate analysis and known risk factors in literature were included in the multivariate logistic regression analysis. Statistical significance was defined at a p value of < 0.05.

Results

Baseline characteristics and simultaneous surgical interventions

Both study cohorts were comparable in terms of donor and recipient characteristics. There were no significant differences in donor age, donor and recipient gender composition, recipient weight and height, recipient body mass index (BMI), ratio of relatives among donor and recipient, proportion and type of dialysis, and time on dialysis before transplantation. Only the recipient age (46.0 ± 11.1) in the ABOi KTx cohort differed significantly compared to 49.5 ± 11.1 in the ABOc KTx cohort ($p = 0.01$) (Table 1). Simultaneous surgical procedures were executed in a similar frequency and proportion in both study cohorts: appendectomy in 2.9% (ABOi) vs. 3.2% (ABOc; $p = 1.0$), nephrectomy of polycystic kidney in 23.1% (ABOi) vs. 26.9% (ABOc, $p = 0.56$), nephrectomy of a former kidney graft in 5.8% (ABOi) vs. 5.6% (ABOc, $p = 1.0$), and nephrectomy of natural kidney in 1.9% (ABOi) vs. 3.1% (ABOc, $p = 0.71$) of the recipients. The duration of DJ maintenance was similar in both cohorts with a mean of 22.5 ± 22.3 days in ABOi KTx cohort vs. 19.3 ± 19.5 days in ABOc KTx cohort ($p = 0.71$).

Short-term patient and graft survival

One-year patient survival rate was not different between ABOi KTx (98.1%) and ABOc KTx (97.5%; $p = 1.0$). The main causes for early death after renal transplantation were severe infections in 3 cases (*C. difficile* colitis in 1 ABOi patient on day 112 and in 1 ABOc patient on day 47 after transplantation and 1 *Aspergillus fumigatus* infection on day 191 after ABOc KTx), a massive myocardial infarction in one ABOi recipient during the first night after transplantation, a severe gastrointestinal bleeding in one ABOc recipient on day 175 and a metastasized urothelium carcinoma in one ABOc patient on day 183 after transplantation. Likewise, delayed graft function (4.8% in ABOi KTx vs. 5.0% in ABOc KTx; $p = 1.0$) and short-term graft survival with 96.2% in ABOi KTx and 94.4% in ABOc KTx ($p = 0.57$) yielded identical results. Even though the graft function rates were slightly lower in the ABOc KTx cohort, a statistically significance was not reached. In the ABOi KTx cohort, the 2 graft losses

Table 1 Baseline characteristics of ABOi and ABOc KTx cohorts

Donor and recipient characteristics at transplantation	ABOi KTx ($n = 104$)	ABOc KTx ($n = 160$)	p value
Donor age (years)	51.3 ± 8.6	51.8 ± 9.0	0.68
Donor gender (female/male)	66 (63.5%)/38 (36.5%)	98 (61.3%)/62 (38.7%)	0.80
Recipient age (years)	46.0 ± 11.1	49.5 ± 11.1	0.01
Recipient gender (female/male)	41 (39.4%)/63 (60.6%)	59 (36.9%)/101 (63.1%)	0.70
Recipient weight (kg)	75.3 ± 15.2	76.7 ± 15.6	0.46
Recipient height (m)	1.75 ± 0.1	1.73 ± 0.1	0.18
Recipient BMI (kg/m^2)	24.6 ± 3.9	25.5 ± 3.9	0.06
Relationship donor/recipient (related/-unrelated)	36 (34.6%)/68 (65.4%)	38 (23.8%)/122 (76.2%)	0.07
Patients on dialysis (no. of patients)	82 (78.8%)	122 (76.3%)	0.66
Time on dialysis (months)	25.2 ± 29.2	21.4 ± 30.2	0.17
Concomitant nephrectomy	32 (30.8%)	57 (35.6%)	0.43
Retransplantation	12 (11.7%)	19 (11.9%)	1.0

Data are n (%) or mean ± SD. p values are estimated with 2-tailed Fisher's exact test for categorical data, and Mann-Whitney *U* test for continuous data

occurred after an arterial thrombosis on day 6 and a chronic humoral rejection on day 119 after transplantation. The 5 recipients in the ABOc KTx cohort lost their graft due to early rejection in three cases on day 1 (two graded as humoral and one as vascular rejection), a venous renal vein thrombosis on day 6 and for unclear reasons in one case after 66 days after transplantation.

Recipients with lymphocele formation ($n = 43$) showed similar 3-year patient and 3-year death-censored graft survival rates compared to recipients without lymphocele formation ($n = 220$) (patient survival 97.6% vs. 96.4%, $p = 1.0$; death-censored graft survival 97.7% vs. 94.8%, $p = 1.0$; Fig. 2).

Lymphocele formation in ABOi vs. ABOc cohort

With a 25.2% incidence ($n = 26$), lymphocele formation was a significantly higher in the ABOi KTx recipients, compared to 10.6% ($n = 17$) in ABOc KTx patients ($p = 0.003$). Independently, the ratio of recipients receiving conservative or surgical treatment was similar in each cohort (conservative treatment: ABOi 38.5% vs. ABOc 35.3%, $p = 1.0$; surgical treatment: ABOi 61.5% vs. ABOc 64.7%, $p = 1.0$). Preoperative dialysis, retransplantation, and simultaneous nephrectomy showed no influence on postoperative development of lymphocele (Table 2).

Sub-group analysis of ABOi KTX recipients

Within the ABOi KTx cohort, the mean number of preoperative immunoadsorption (IA) and/or plasmapheresis (PP) sessions was slightly but not significantly higher in recipients developing a postoperative lymphocele compared to those without occurrence of lymphocele (recipients with lymphocele formation ($n = 26$): 7.73 ± 5.06 IA/PP sessions; recipients without lymphocele formation ($n = 77$): 5.92 ± 3.54 IA/PP sessions, $p = 0.148$) (Fig. 3a). Interestingly, in patients with the need for surgical treatment, the mean number of preoperative IA/PP sessions even peaked with 8.88 ± 5.89 ($n = 16$) and was not significant ($p = 0.097$), whereas recipients with conservative treatment ($n = 10$) needed a mean number of preoperative IA/PP sessions of 5.9 ± 2.69 and therefore showed similar results than patients without lymphocele formation ($p = 0.718$). Due to low numbers of cases, the comparison between the conservative versus the surgical treatment sub-group was not significant with a p value of 0.328 (Fig. 3b).

In general, recipients with ≥ 8 preoperative IA/PP sessions appeared to be at risk for developing a lymphocele (40.0% vs. 19.2%; $p = 0.044$) (Fig. 4a). With 87.5% ($n = 7/8$) vs. 50% ($n = 9/18$, $p = 0.099$) the proportion of surgically treated recipients was higher for patients receiving ≥ 9 preoperative IA/PP sessions, although this difference was not significant (Fig. 4b).

Recipients with a preoperative IA/PP session on the day of transplantation ($n = 63$) showed no higher risk of lymphocele formation (28.6% vs. 20.0%, $p = 0.362$) (Fig. 5a). Likewise, postoperative IA/PP sessions (in $n = 29$ recipients) did not affect the proportion of lymphocele formation (24.1% vs. 25.7%, $p = 1.0$) (Fig. 5b).

Analysis of potential risk factors for lymphocele formation

In a multivariate logistic regression analysis of possible independent risk factors for lymphocele formation, the affiliation to the ABOi cohort showed a highly significant difference with a p value of 0.008 (OR 2.56, 95% CI 1.28–5.12). Particularly, recipients receiving ≥ 8 IA/PE preoperatively demonstrated a significantly higher risk (OR 5.61, 95% CI 2.31–13.61, $p < 0.001$). In recipients with ≤ 7 IA/PE sessions, results were below the significance threshold (OR 2.00, 95% CI 0.93–4.31, $p = 0.078$). All other analyzed variables including recipient age and BMI, relationship donor/recipient, retransplantation, preemptive transplantation, simultaneous nephrectomy, delayed graft function, and duration of DJ maintenance were insignificant (Table 3).

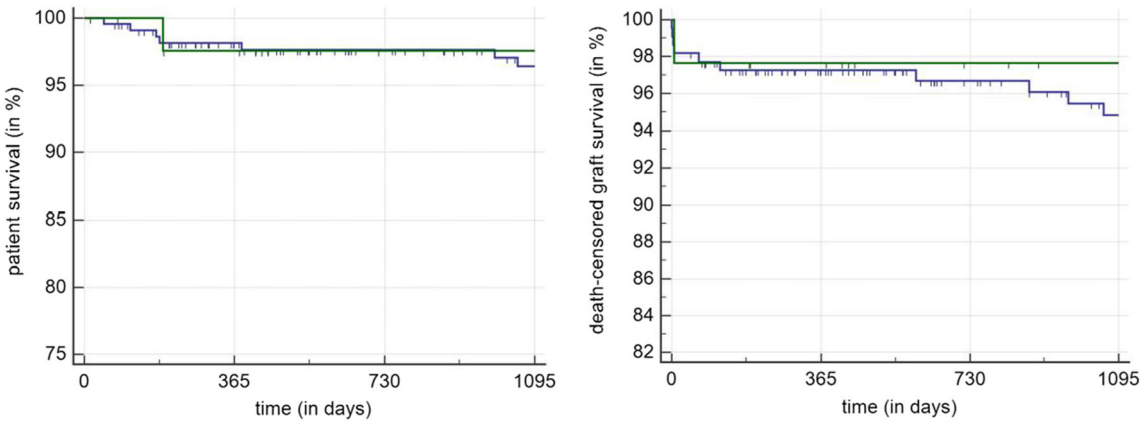

Fig. 2 Three-year patient and death-censored graft survival: (blue) recipients without lymphocele formation ($n = 220$); (green) recipients with lymphocele formation ($n = 43$)

Table 2 Analysis of potential risk factors for lymphocele development in addition to blood group incompatibility

Potential factors	ABOi KTx ($n = 103$)		p value	ABOc KTx ($n = 160$)		p value
	$n =$	Lymphocele		$n =$	Lymphocele	
Pre-emptive transplantation (%)	21	3 (14.3%)	0.27	38	5 (13.4%)	0.56
Recipients on dialysis (%)	82	23 (28.1%)		122	12 (9.8%)	
Retransplantation (%)	12	3 (25.0%)	1.0	19	2 (10.5%)	1.0
First transplantation (%)	91	23 (25.3%)		141	15 (10.6%)	
Simultaneous nephrectomy (%)	31	5 (16.1%)	0.22	57	4 (7.0%)	0.42
No simultaneous intervention (%)	72	21 (29.2%)		103	13 (12.6%)	

Data are n (%). p values are estimated with 2-tailed Fisher's exact test for categorical data

Discussion

In Germany, for numerous end-stage renal disease patients, ABO-incompatible renal transplantation constitutes a valued supplementary therapeutic option to expand the live donor pool and for many of these the only possibility to perform an early or even pre-emptive living donor kidney transplantation. While former studies discarded doubts concerning long-term patient and graft survival [1–6], we still lack of knowledge concerning the rates of postoperative surgical complications, possibly caused by the intensive preoperative immunotherapy. Our study cohort, including 104 consecutive ABOi KTx recipients, represents one of the largest single-center cohorts based on a preliminary rituximab and immunoadsorption protocol.

In general, data on surgical complications after ABOi KTx are rather scarce and are mainly centered on the bleeding risk after ABOi KTx [8–12, 15]. To date, lymphocele formation after ABOi KTx has practically never been analyzed prior to this study. Historically, the incidence of lymphocele formation after renal transplantation is specified between 2.2% and 17.3% [16–18]. Our data showed a significantly higher risk for ABOi recipients with 25.2% vs. 10.6% in the blood group compatible cohort. Independently of the cohort, in about one third of patients, conservative treatment with maintenance of the double-J (DJ) stent (if still in situ) until spontaneous remission was favorable. For the main part of both cohorts, the necessity for surgical intervention persisted. The treatment options of lymphoceles are sufficiently described [18, 19] and is mainly a laparoscopic procedure. In contrast, Bennani et al. did not experience a difference in the development of lymphoceles in their matched pair analysis published in 2016 ($n = 44$). After administration of rituximab 30 days preoperatively, unlike our immunosuppressive protocol, only a dual immunosuppressive therapy combining prednisone and

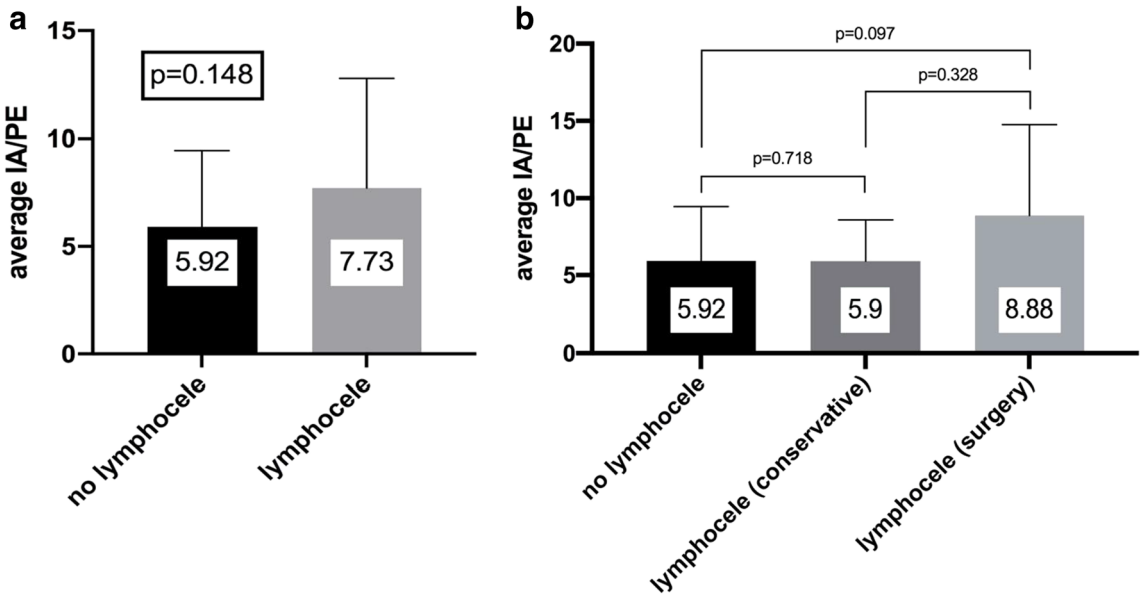

Fig. 3 **a** Mean number of preoperative IA/PP sessions: (a) ABOi recipients without postoperative lymphocele 5.92 ± 3.54 ($n = 77$); (b) ABOi recipients with postoperative lymphocele 7.73 ± 5.06 ($n = 26$). **b** Mean number of preoperative IA/PP sessions: (a) ABOi recipients without postoperative lymphocele 5.92 ± 3.54 ($n = 77$); (b) ABOi recipients with postoperative lymphocele (conservative treatment) 5.9 ± 2.69 ($n = 10$); (c) ABOi recipients with postoperative lymphocele (surgical treatment) 8.88 ± 5.89 ($n = 16$). ABOi ABO-incompatible, IA immunoadsorption, PP plasmapheresis

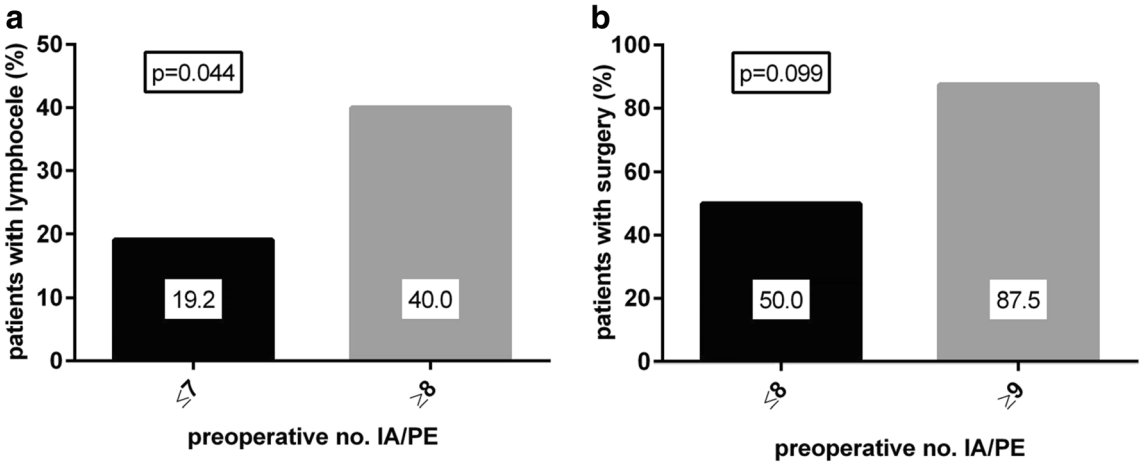

Fig. 4 **a** Percentage of recipients with postoperative lymphocele formation: (a) ABOi recipients receiving ≤ 7 preoperative IA/PP sessions (n =); (b) ABOi recipients receiving ≥ 8 preoperative IA/PP sessions (n =). **b** Percentage of recipients with surgically treatment of lymphocele: (a) ABOi recipients receiving ≤ 8 IA/PP sessions (n = 18); (b) ABOi recipients receiving ≥ 9 IA/PP sessions (n = 8). ABOi ABO-incompatible, IA immunoadsorption, PP plasmapheresis

tacrolimus or mycophenolate mofetil was applied in their study, beginning 12 days preoperatively [20]. In a Korean study (ABOi: n = 95; ABOc: n = 121) published recently, similar results were reported. During the preoperative phase, the immunosuppressive protocol significantly differed compared to ours, as only an exclusive, lower dose of mycophenolate mofetil (1–1.5 g/day), was administered 7 days prior to transplantation [21]. The influence of immunosuppressive medication on the incidence of surgical complications has already received attention [22–24]. Specifically, the impact of mycophenolate mofetil and mTOR inhibitors seems to be a conceivable approach. As described by Lopau et al., mycophenolate mofetil has a negative effect on the incidence of developing postoperative lymphoceles [24]. It is speculated that preoperative administration of mycophenolate mofetil actually increases this effect in ABOi KTx recipients. Since none of our analyzed recipients received an mTOR-based immunosuppression, a negative influence is virtually excluded.

Multiple medical risk factors, including DGF, duration of dialysis, retransplantation, acute rejection, recipient age, and recipient BMI, are associated with a significantly higher rate of lymphocele formation [25–30]. An impact of these factors on the results is questionable, since the baseline characteristics of both, ABOi and ABOc KTx cohorts, did not show any remarkable differences with the only exception of a slightly higher recipient age in the ABOc cohort, rather favoring lymphocele formation in the ABOc recipients. A possible explanation for this age difference might be a somewhat higher, statistically insignificant fraction of unrelated relationship between donor and recipient, probably caused by a higher fraction of partners donating kidneys in the ABOc KTx group. This difference is likely due to the fact, that in our center living

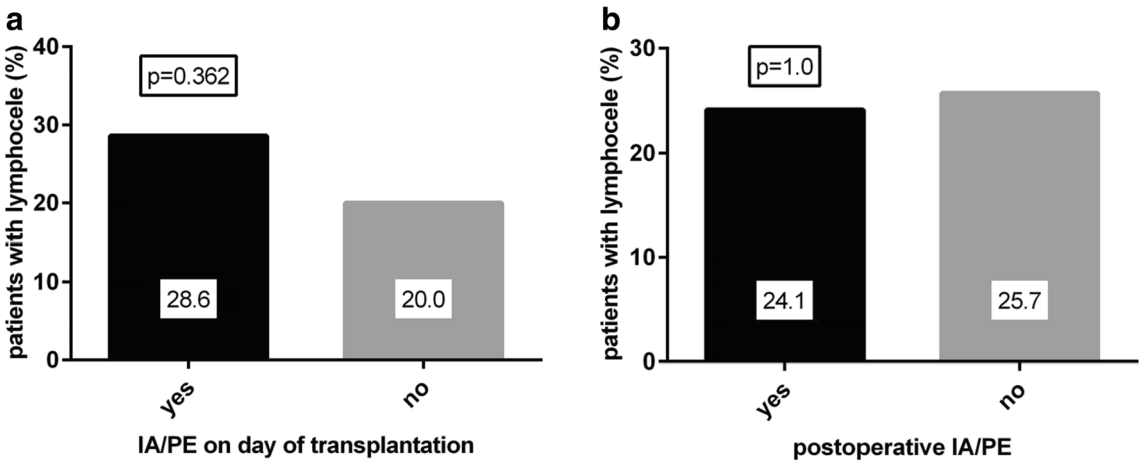

Fig. 5 **a** Influence of directly preoperative IA/PP on lymphocele formation: (a) ABOi recipients with preoperative IA/PE on day of transplantation (n = 63); (b) ABOi recipients without preoperative IA/PE on day of transplantation (n = 40). **b** Influence of postoperative IA/PP on lymphocele formation: (a) ABOi recipients with postoperative IA/PE (n = 29); (b) ABOi recipients without postoperative IA/PE (n = 74). ABOi ABO-incompatible, IA immunoadsorption, PP plasmapheresis

Table 3 Multivariate regression analysis to identify independent risk variables for lymphocele formation

Potential factors	Odds ratio (95% CI)	Significance
ABO-incompatible transplantation	2.56 (1.28–5.12)	0.008
ABOi KTx ≤ 7 IA/PE sessions	2.00 (0.93–4.31)	0.078
ABOi KTx ≥ 8 IA/PE sessions	5.61 (2.31–13.61)	< 0.001
Recipient age	1.00 (0.96–1.04)	0.93
Recipient BMI	0.97 (0.88–1.06)	0.48
Relationship donor/recipient	1.39 (0.57–3.41)	0.47
Pre-emptive transplantation	0.95 (0.38–2.36)	0.91
Retransplantation	0.89 (0.28–2.82)	0.85
Simultaneous nephrectomy	0.49 (0.21–1.15)	0.10
Delayed graft function	0.35 (0.04–2.94)	0.33
DJ duration > 15 days	1.58 (0.76–3.32)	0.22

donor kidney transplantation in immunological low risk constellations between donors and recipients (1st degree blood relationship, HLA mismatch ≤ 3, no preexisting panel reactive antibodies (PRA) and 1st transplantation) are performed without using immunosuppressive induction therapy. Hence, numerous ABOc KTxs' between parents and descendants or siblings were excluded from our analysis in respect to a different immunosuppressive regimen. Likewise, the minor, insignificantly higher BMI in the ABOc cohort, would rather increase the incidence lymphoceles in ABOc recipients. Concerning the remaining medical risk factors, an influence on lymphocele formation is implausible, since the occurrence of DGF was rare, the mean preoperative time on dialysis was extremely short and the incidence of acute rejection episodes equally, as reported in a former publication [1]. In recipients receiving a retransplantation or simultaneous nephrectomy, the multivariate logistic regression analysis clearly showed no higher risk for the development of lymphoceles. Finally, ABOi KTx and especially numerous preoperative IA/PE sessions remain the only independent risk factors leading to a significant higher rate of lymphocele formation in ABOi KTx in our analysis.

The specific influence of immunoadsorption or plasmapheresis on the incidence of lymphoceles remains unresolved. In our cohort, the mean preoperative number of IA/PP sessions seemed to be slightly but not significantly higher in the subcohort of recipients developing a postoperative lymphocele. In recipients receiving ≥ 8 IA/PP sessions, the risk for postoperative lymphocele was significantly increased. A statement in favor of one type of treatment (IA or PP) is currently impossible. Preoperative IA was performed in all ABOi recipients, with a few receiving additionally PP, when target titer values were not achieved. The kind of IA (Glycosorb A/B™ vs. Immunosorba™) is irrelevant with regard to postoperative complication rates [31]. Yet, an exact mechanism of IA/PP leading to an increase of lymphocele formation is completely unresolved. One assumption might be an altered blood coagulation after the IA/PP sessions. Two publications reported a correlation between blood coagulation disorders and a low molecular weight heparin prophylaxis with a higher incidence of lymphoceles [32, 33]. Koessler et al. reported a 50–70% decrease of blood coagulation factors after PP. However, on some blood coagulation factors e.g. fibrinogen IA has a similar effect [34]. This impaired blood coagulation might trigger lymphocele formation in ABOi KTx by decelerating lymphatic vessel occlusion.

Conclusion

ABOi KTx recipients are at an increased risk for postoperative lymphocele formation with the need for further intervention or even surgical revision, compared to ABOc recipients. The threshold of > 7 IA/PP sessions seems to increase the risk of lymphocele formation clearly. In these ABOi KTx recipients, prophylactic peritoneal fenestration during transplantation might be favorable.

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Author contributions BMJ: study conception and design, drafting of manuscript, interpretation of data, transplant surgeon. CS: acquisition of data. TG: analysis of data. OT: critical revision of manuscript. CL: critical revision of manuscript. SFF: critical revision of manuscript. SZ: study conception and design, critical revision of manuscript. PP: critical revision of manuscript, principal transplant surgeon.

Compliance with ethical standards The registry and the study were approved by the ethics committee of the University Medical Center Freiburg and in accordance with the Declaration of Helsinki.

All patients of the Freiburg living donor kidney program gave informed consent for collecting and storing their data in our living donor transplant registry for analysis for research purposes.

Conflict of interest The authors declare that they have no conflict of interest.

Abbreviations *ABOc,* blood group compatible; *ABOi,* blood group incompatible; *BMI,* body mass index; *CMV,* cytomegalovirus; *DJ,* double-J catheter; *EC,* red blood cell transfusion; *IA,* immunoadsorption; *KTx,* kidney transplantation; *PP,* plasmapheresis; *PRA,* panel reactive antibody; *USRDS,* United States Renal Data System

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