Risk Factors for Graft Loss Due to Acute Vascular Complications in Adult Renal Transplantation Using Grafts Without Vascular Anomalies

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ABSTRACT

Background. Vascular complications are the main cause of early graft loss in renal transplant (RT). A graft with multiple vessels represents the most validated risk factor. The aim of the present study was to identify potential predictive factors for acute vascular complications causing graft loss when graft vascular anomalies are excluded.

Methods. This is a retrospective case-control (1:3 ratio) study extrapolated from the RT series of the Renal Transplant Unit - Udine University Hospital, during the period 1993-2017. Grafts with multiple vessels and retransplant cases were excluded.

Results. The overall prevalence of graft loss due to acute vascular complications was 2.6% (25/961). Seventeen complicated recipients had grafts without vascular anomalies (case group). The median time between RT and complication was 6 days (interquartile range, 4-23 days). The following types of vascular complications were recorded: 5 isolated renal artery thromboses (0.5%), 4 isolated renal vein thromboses (0.4%), 4 combined renal artery and vein thromboses (0.3%), 3 renal artery ruptures due to mycotic arteritis (0.3%), and 1 renal artery nonmycotic pseudoaneurysm (0.1%). No differences were recorded between the groups in terms of donors and grafts characteristics. Complicated recipients showed a statistically higher prevalence of thromboembolism history ($P = .046$) and vascular atherosclerosis ($P = .048$). During the postoperative course, blood stream infections ($P = .02$), acute rejection ($P = .03$), bleeding from a nonmacrovascular source ($P = .04$), and multiple reintervention because of nonvascular complications ($P = .03$) were identified as significant risk factors.

Conclusions. Recipient characteristics and post-RT complications rather than donor and graft characteristics are relevant risk factors for graft loss due to acute vascular complications when graft vascular anomalies are excluded.

VASCULAR complications represent the main cause of early graft loss [1,2]. They may affect the graft vein, the graft artery, and/or the recipient vessels and may develop as thrombosis, stenosis, bleeding, aneurysm, or pseudoaneurysm with possible rupture or arteriovenous fistula formation [3]. The reported prevalence ranges from 1% to 23% [2,4].Graft vascular anomalies with multiple vessels [2,5,6] represent the most frequently investigated and validated risk factors for vascular complications. It might be expected that they act in the pathogenesis of vascular complication by multimodal mechanisms. The aim of the present study was to identify potential predictive factors for acute vascular complications causing graft loss when graft vascular anomalies are excluded.

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MATERIALS AND METHODS

This is a retrospective case-control study extrapolated from the clinical series performed at the Renal Transplant Unit of the University Hospital of Udine during the period 1993-2017. From a prospectively maintained electronic database the cases of graft loss with urgent graft nephrectomy due to acute vascular complications were selected, representing the study group (complication group). Acute vascular complications were defined as any case of acute-onset complication affecting the graft renal artery and/or vein that was clinically suspected on the basis of symptoms, laboratory test, and/or Doppler ultrasonography and was confirmed by computed tomography angiography scan and/or angiography. The final diagnosis was established at pathologic examination of the explanted graft. Exclusion criteria were retransplant, grafts with multiple vessels, short renal vein without extension of a donor vena cava, cases successfully treated with endovascular procedures, or cases of renal artery stenosis. For the control group, a 3:1 ratio was used, and uncomplicated patients receiving grafts without multiple vessels or short renal veins were randomly selected under the condition that the transplant was undertaken in the same year as the corresponding study case. Demographic and clinical data of the donors, recipients, intraoperative course, and postoperative course were reviewed and recorded. All grafts were procured from brain-dead heart-beating donors. All renal transplant (RT) procedures used the right or left iliac fossa via an extraperitoneal approach as implantation site. The renal graft vessels were anastomosed end-to-side to the recipient's external iliac vessels with Prolene 5-0 running sutures. A Lich-Gregoir technique over a double J temporary ureteral stenting was used for ureteroneocystostomy. Induction immunosuppressive therapy was performed with basiliximab or rabbit antithymocyte globulin (Thymoglobulin). Baseline triple immunosuppression included calcineurin inhibitor (either cyclosporine or tacrolimus), antimetabolite (mycophenolate sodium or mycophenolate mofetil), and steroids. Heparin (Calciparine) 5000 UI $\times$ 2/d was used as thromboprophylaxis until postoperative day (POD) 10 and thereafter switched to low-dose aspirin. Standard post-transplant management for clinical surveillance over postoperative complications was based on daily laboratory tests including full blood count as well as kidney function for the first 10 PODs and thereafter as needed according to the clinical course. Doppler ultrasonography of the graft was routinely performed every day up to POD 7 and thereafter when clinically indicated. The following postoperative variables were investigated as potential predictors of vascular complications: early acute rejection that was biopsy proven and time limited to the first 6 months after RT; delayed graft function (DGF), defined as need for dialysis in the first postoperative week; urologic complications, which were any case of urine leak or ureteric stricture due to any underlying cause; bleeding that was secondary to a non-macrovascular source, usually, from the graft surface or surrounding adipose-lymphatic tissue; lymphocele, which was any case of lymphatic collection around the graft either causing symptoms, hydronephrosis, or worsening renal function; urinary tract infection that was culture proven; and blood stream infection that was culture proven.

In the study group, postoperative clinical events that occurred after the development of the vascular complications were not considered, and the time limit for the occurrence of vascular complication was 3 months. Consequently, 3 months was also the selected time frame for the control group for the recording of any postoperative event.

Categorical variables and frequencies were expressed by percentage, while continuous variables were expressed by mean (SD) or median (interquartile range), as appropriate. For categorical variables, cross-tabulations were generated, and χ^2 or Fisher exact test was used to compare distributions. For continuous variables t test or Mann-Whitney test was used. Logistic multivariate stepwise analyses was used for all variables preliminary significant at $P \leq .05$.

RESULTS

A total of 961 patients were submitted to RT during the study period. In 25 cases an acute vascular complication requiring graft nephrectomy occurred, with an overall prevalence of 2.6%. Among these, 8 patients were excluded because of presence of graft with multiple vessels. Therefore, the resulting study population included 17 complicated cases and 51 control cases. In the complicated group the following acute vascular complications were recorded: 5 isolated renal artery thromboses (0.5%), 4 isolated renal vein thromboses (0.4%), 4 combined renal artery and vein thromboses (0.3%), 3 renal artery ruptures due to mycotic arteritis (0.3%), and 1 renal artery nonmycotic pseudoaneurysm (0.1%). No cases of vascular twisting or kinking nor of major bleeding from a macrovascular source were detected. In presence of graft arterial complication, the native iliac artery was involved in 4 cases (0.4%). The median time interval between RT and complication was 6 days (interquartile range, 4-23 days). The demographic and clinical data of recipients and postoperative details in the control group and study group are summarized in Table 1. The complication and control groups were homogeneous in terms of donor age, cold ischemia time, warm ischemia time, graft type, and site of graft implant. No differences in terms of immunosuppressant therapy were noted since both groups were treated with the same protocol. Conversely, among the recipients' demographic and clinical characteristics, a statistically higher prevalence of a thromboembolism history ($P = .046$) and of vascular atherosclerosis ($P = .048$) in the complication group were recorded. No cases of intraoperative hemodynamic instability were recorded. During the postoperative course, the complication group was associated with a higher incidence of blood stream infections ($P = .02$), acute rejection ($P = .03$), bleeding from a nonmacrovascular source ($P = .04$), and multiple reintervention because of nonvascular complications ($P = .03$). In logistic multivariate analysis, blood stream infection (odds ratio, 5.02; 95% CI, 1.29-19.49; $P = .02$) was shown to be the only independent risk factor for graft loss due to acute vascular complications.

DISCUSSION

The prevalence of early vascular complications in the present series was in line with the data reported in literature: 0.2% to 7.5% or 0.5% to 3.5% for renal artery thrombosis [3,5], 0.1% to 8.2% or 0.5% to 4% for renal vein thrombosis [3,5] and $< 1\%$ for mycotic or nonmycotic pseudoaneurysm [6]. The most frequently reported risk factors for vascular complications related to the recipients' characteristics are advanced age, vessel atherosclerosis, obesity, diabetic

Table 1. Demographic and Clinical Data of Recipients With Graft Loss Due to Acute Vascular Complications (Complicated Group) and Uncomplicated Recipients (Control Group)

	Complicated Group (n = 17)	Control Group (n = 51)	*P* Value
Sex, M:F	7:10	30:21	.21
Age, mean (SD), y	55.6 (10.1)	54.6 (10.9)	.75
BMI, mean (SD)	25.6 (4.6)	25.3 (4.1)	.58
Diabetes mellitus, No. (%)	2 (11.7)	7 (13.7)	> .99
Cardiopathy, No. (%)	2 (11.7)	11(21.6)	.49
History of coronary angioplasty, stenting, bypass, No. (%)	1 (5.9)	4 (7.8)	> .99
Cerebrovascular disease, No. (%)	4 (23.5)	3 (58.8)	.06
Vessels atherosclerosis, No. (%)	5 (29.4)	5 (9.8)	.048*
History of thromboembolism, No. (%)	3 (17.6)	1 (2.0)	.046*
Hyperparathyroidism, No. (%)	3 (17.6)	6 (11.7)	.68
Rheumatologic disease, No. (%)	2 (11.8)	4 (7.8)	.64
HBV, HCV infection, No. (%)	2 (11.8)	5 (9.8)	> .99
Polycystic kidney disease, No. (%)	1 (5.9)	7 (13.7)	.67
Type of dialysis, No. (%)			
Hemodialysis	10 (58.8)	33 (64.7)	.66
Peritoneal dialysis	7 (41.2)	18 (35.3)	
Time of dialysis, median (IQR), y	3 (2-5)	3 (2-5)	.43
PRA, median (IQR)	0 (0-0)	0 (0-0)	.42
HLA compatibility, median (IQR)	1 (1-2)	1 (2-3)	.27
Delayed graft function, No. (%)	6 (35.3)	15 (22.0)	.06
Acute rejection, No. (%)	4 (23.5)	2 (3.9)	.03*
Urinary tract infection, No. (%)	5 (29.4)	10 (19.6)	.50
Blood stream infection, No. (%)	6 (35.3)	5 (9.8)	.01*
Urologic complications, No. (%)	2 (11.8)	4 (7.8)	.64
Lymphocele, No. (%)	4 (23.5)	6 (11.7)	.25
Bleeding, No. (%)	5 (29.4)	4 (7.8)	.04*
Single reintervention for nonvascular complications, No. (%)	5 (29.4)	6 (11.7)	.09
Multiple reinterventions for nonvascular complications, No. (%)	4 (23.5)	2 (3.9)	.03*

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; PRA, panel-reactive antibody.
*$P < .05$.

nephropathy, hypertensive nephropathy, history of thromboembolism, systemic lupus erythematosus, and peritoneal dialysis [1–4,7–9]. Despite clinical diversification, such factors directly or indirectly share some pathogenic features: atherosclerosis and/or hypercoagulative state [8]. Under this perspective, the results of the present study identifying an history of thromboembolism and arterial atherosclerosis appear in line with the literature. No specific guidelines are currently available either on an appropriate pre-RT screening for congenital and acquired thrombophilia or on an optimal prophylaxis in the peritransplant period [1,7]. Several studies have investigated different screening and anticoagulation protocols, but the results are heterogeneous [7]. For recipients' arterial atherosclerosis, there are no recommendations for any specific selection criteria apart from a relative contraindication in presence of severe atherosclerosis [10]. Some studies have reported on the feasibility of RT in patients with severe aortoiliac atherosclerosis by performing concomitant iliac angioplasty, aortoiliac bypass, or iliac reconstruction using a synthetic prosthesis or a fresh arterial graft [10]. However, these procedures present a certain grade of technical complexity and require high expertise. Regarding the effect of postoperative events on the risk of developing an acute vascular complication, the available data are limited. The currently identified negative predictors comprise DGF, perioperative hemodynamic instability, immunosuppression therapies, and acute rejection [3].In the present study we did not have cases of intraoperative hemodynamic instability, and the immunosuppression regimen was similar for all the patients. Allografts with multiple vessels compared with those with single vessels are at higher risk of DGF [6]. This may explain why in the present study DGF was not a significant factor. Conversely, it registered a statistically higher prevalence of blood stream infections, postoperative bleeding, acute rejection, and necessity of reinterventions in patients who afterward developed an acute vascular complication. Blood stream infection has been identified as an independent risk factor for long-term graft survival [11], but a direct correlation with vascular complications has never been reported. Perioperative transfusions and acute rejection have been already associated with postoperative surgical complications [4] and vascular complications [5], probably sharing an immunologic mechanism. Furthermore, perioperative transfusion clearly correlates with bleeding in the kidney graft area. This complication in turn may potentially determine a need of reintervention, hemodynamic instability, or extrinsic compression on graft parenchyma and

vessels, thus predisposing for vascular complications [9,12]. Overall, RT recipients show a persistent inflammatory state associated with an acquired thrombophilia by higher levels of fibrinogen, d-dimer, prothrombin activation fragment F 1 + 2, and interleukin 6, and lower levels of protein S while sepsis, surgery, bleeding, and rejection are known potential triggers for hypercoagulative states [7]. Therefore, it may be speculated that one of the possible underlying mechanism associating such postoperative events with the occurrence of graft vascular complications may be a precipitating effect on a chronic prothrombotic RT recipient's state.

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