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ORIGINAL ARTICLE

Renal transplant and hemostasis: early postoperative changes in recipients and donors

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Abstract

Background: The benefit of administering pharmacologic thromboprophylaxis following renal transplantation remains uncertain.

Objectives: To compare hemostatic parameters before and after renal transplant surgery in both recipients and their donors at predetermined time points.

Methods: Blood samples were collected at baseline (T1), immediately after surgery (T2), and at 24 hours after surgery (T3) in both recipients and donors and at 72 (T4) and 120 hours (T5) from recipients only. Assays included *in vitro* thrombin generation, factor VIII (FVIIIc) activity, von Willebrand factor (VWF) antigen, D-dimer, antithrombin activity, prothrombin fragment 1 + 2 (F1 + 2), thrombin-antithrombin complexes, and plasminogen activator inhibitor-1 (PAI-1) antigen.

Results: Fifty-two patients (28 recipients and 24 donors) were enrolled. Both donors and recipients had increased FVIIIc, VWF, F1 + 2, D-dimer, and PAI immediately after surgery but reduced antithrombin. Mixed-model analysis showed that the magnitude of change over time (between T1 and T3) for FVIIIc (mean estimated difference [MED], 72; 95% CI, 41-102; $P < .0001$), VWF (MED, 89; 95% CI, 35-142; $P = .001$), F1 + 2 (MED, 283; 95% CI, 144-422; $P < .0001$), thrombin-antithrombin complexes (MED, 3.5; 95% CI, 1.9-5.1; $P < .0001$), D-dimer (MED, 2.2; 95% CI, 1.0-3.3; $P < .0001$), PAI-1 (MED, 9.2; 95% CI, 3.4-14.9; $P = .002$), and time to peak thrombin generation (MED, 1.5; 95% CI, 0.35-2.7; $P = .01$) was more significant in recipients than in donors.

Conclusion: Persistence of a hypercoagulable state was more prominent in recipients after 24 hours despite recovery in renal function and initiation of thromboprophylaxis.

KEYWORDS
hemostasis, recipients, renal transplant, thrombin generation, thromboprophylaxis

Essentials

- Patients with chronic kidney disease are at increased risk for clotting and bleeding complications.
- There are differences in coagulation between recipients and donors at baseline and in the early postoperative period.
- Risk of clotting is notable in recipients compared to that in donors despite recovery in renal function.
- Relevant data are required to support larger studies to inform thromboprophylaxis guidelines.

1 | INTRODUCTION

The treatment of choice for patients with end-stage renal disease, defined as reduction in glomerular filtration rate to <15 mL/min/1.73 m^2, is renal transplantation. Advances in surgical techniques and improvements in immunosuppression have contributed to increased numbers of renal transplants being performed annually worldwide [1–3].

Patients with chronic kidney disease (CKD) have an altered hemostatic state and are at risk of developing both thrombotic and bleeding complications due to increase in prothrombotic/antifibrinolytic factors (factor [F] VIII activity; von Willebrand factor [VWF], however, with the exact mechanisms not yet elucidated; and plasminogen activator inhibitor type 1), platelet dysfunction induced by uremic toxins, and presence of anemia and thrombocytopenia [4–6]. The process of transplant surgery further increases these risks [5,7].

There is growing literature to support an increased risk of venous thromboembolism (VTE) in patients with reduced estimated glomerular filtration rate (eGFR) (<45 mL/min/0.73 m^2) [8]. The incidence of VTE and early postoperative bleeding in patients with renal transplant not receiving chemical thromboprophylaxis (TP) has been reported as 1.7% to 4.5% [9] and 2.1% to 5.2%, respectively [10,11]. One of the main concerns following renal transplant surgery is the risk of renal artery or renal vein thrombosis, which can result in early renal graft losses, with some studies reporting an incidence as high as 40% without TP [12].

The benefit of administering pharmacologic VTE prophylaxis following renal transplantation remains uncertain, as highlighted in a recent systematic review. In this systematic review, 13 studies with 1600 patients revealed a wide variation in type of TP used, time of onset, dosing, and duration. When comparing TP to no intervention, there was no statistically significant reduction in thrombosis risk (risk ratio, 0.2; 95% CI, 0.01-4.63), but of note, all studies included in the analyses were underpowered to answer this question [13].

Better understanding of hemostatic changes during and after renal transplant surgery may assist in determining the risks and benefits of TP. Although some studies have evaluated these changes [14,15], to our knowledge, none has examined them in the immediate postoperative period or assessed if improvement in renal function in recipients reverses the hemostatic imbalance seen in these patients.

The aim of this study was to compare changes in hemostatic parameters before and after renal transplant surgery in both recipients and their donors at predetermined time points in the perioperative period.

2 | METHODS

This was a prospective single-site cohort study with collection of blood samples from consecutive recipients of live renal transplants and their respective donors over a 15-month period (July 2018-September 2019). The clinical care of recipients and donors was not altered for the purpose of this study. The study received approval by the local research ethics committee and Health Research Authority (integrated research application system number 246513). Prior to enrollment, written informed consent was obtained from both recipients and donors. Patients undergoing deceased donor transplantation were excluded.

Clinical information and results of routine laboratory tests (hematology and biochemistry) were collected using electronic patient hospital records.

2.1 | Research blood sample collection and processing

Venous blood samples (15 mL each time) were collected from both recipients and donors at the following time points: at baseline, immediately prior to surgery (T1), immediately after surgery and within 2 hours of surgical site closure (T2), and at 24 hours after surgery (T3). For recipients only, additional blood samples were collected at 72 (T4) and 120 hours (T5) after surgery.

Samples were collected in 5-mL BD vacutainers (BD Diagnostics, each containing 0.5 mL of 0.109M buffered trisodium citrate at a ratio of 1 part of anticoagulant to 9 parts of blood). Samples were processed within 30 minutes of collection by double centrifugation at 2000 *g* for 12 minutes to prepare platelet-poor plasma, which was stored in aliquots at −70 ± 10 °C until further testing.

2.2 | Surgical details

Surgery in all patients was performed using a similar surgical technique. In summary, retrieval of the kidney from living donors was performed using the hand-assisted laparoscopic technique. "Bench-side preparation" of retrieved kidney graft involved perfusing it with a cold preservative solution to cool it down to 4 °C for static cold storage before implantation. The vessels and ureter were also prepared for anastomoses. In the recipient, the kidney was implanted in the iliac fossa, with the existing kidneys left *in situ*. The donor kidney artery and vein were anastomosed to the external iliac artery and vein, respectively. Once anastomosis was completed, the kidney was reperfused, and the transplanted organ was examined for adequate perfusion. The ureter was then anastomosed to the bladder once perfusion was satisfactory, and hemostasis was achieved. In select cases, at the surgeon's discretion, a bolus of unfractionated heparin (UFH; variable dose) was administered; this occurred when there was concern that the kidney was not well perfused due to microthrombi from inadequate flushing either during organ retrieval from the donor or at bench-side preparation before transplantation.

2.3 | Perioperative treatment

Recipients were started on an immunosuppressive medication regimen just prior to surgery. Most received induction therapy with the IL-2 inhibitor basiliximab and maintenance therapy with tacrolimus, mycophenolate mofetil, and prednisolone.

All patients were risk assessed for postoperative TP, and if there was no contraindication, TP with 4500-IU tinzaparin daily was administered between 26 and 28 hours after surgery in recipients and between 8 and 10 hours after surgery in donors. All participants wore antiembolic stockings after surgery. Prophylaxis (both mechanical and pharmacologic) continued until hospital discharge, which was a median duration of 5 days for recipients and 3 days for donors. In addition, recipients were also started on low-dose aspirin (75 mg daily) at hospital discharge, which continued for at least 1 month.

2.4 | Laboratory assays

Unless specified, all laboratory assays were performed following the laboratory's standard operating procedures. Full blood counts were analyzed on automated Sysmex XN analyzers, and measurements of prothrombin time (PT), activated partial thromboplastin time (APTT), 1-stage FVIII activity, VWF antigen, D-dimer, and antithrombin (AT) activity were performed on a Sysmex CS5100 analyzer.

Prothrombin fragment 1 + 2 (F1 + 2) and thrombin-antithrombin (TAT) complexes were assayed using Siemens Enzygnost enzyme-linked immunosorbent assay kits following the manufacturer's instructions. The plasminogen activator inhibitor-1 (PAI-1) antigen was assayed using a Hyphen BioMed manual ELISA kit following the manufacturer's instructions.

Creatinine and albumin were analyzed using spectrophotometry on a Roche Cobas 8000 analyzer, and eGFR was mathematically derived using serum creatinine, age, and sex.

2.5 | *In vitro* thrombin generation

The calibrated automated thrombogram method, described by Hemker et al. [16], was used to perform the thrombin generation (TG) assay. The manufacturer's platelet-poor plasma reagents, which gave a reaction concentration of 5 pM for tissue factor (TF) and 4 mM for phospholipids (Thrombinoscope BV), were used. All patient samples were tested in triplicate.

2.6 | Statistical analysis

No formal sample size calculation was performed as this was a descriptive laboratory study. Descriptive results are presented as frequencies (proportions) or medians (with interquartile range) as appropriate. The Mann–Whitney U-test was used to compare continuous variables between the 2 groups at baseline (T1). Changes over time in both donors and recipients are presented as differences between the postsurgery time points and presurgery (or baseline) measurements. The Wilcoxon signed-rank test was used to compare changes over time in recipients (ie, from T1 to T2, T1 to T3, T1 to T4, and T1 to T5) and donors (ie, from T1 to T2 and T1 to T3). For hemostatic variables in which significant differences were noted in changes over time within the recipient group by Wilcoxon test, a mixed-effects regression model with group and time points as covariates was used to determine if there was an interaction between continuous variables between recipient and donor groups over time (from T1 to T3). Tests were 2 tailed at the 5% level of statistical significance. Analysis was performed using SPSS (IBM SPSS Statistics for Macintosh, version 26.0) and GraphPad software version (GraphPad software, Inc).

3 | RESULTS

A total of 78 patients were assessed for eligibility, and of them, 52 (66.7%, 28 recipients and 24 donors) provided informed consent to participate (Figure). Of 19 patients who declined to participate, 15 (78.9%) were recipients, with the most common reason being anxiety prior to the procedure.

It was not possible to collect blood samples from all participants at all different time points, with the 2 main reasons for this being difficulty in bleeding participants and refusal to be bled (eg, being in pain and, therefore, unable to tolerate additional venesection where required).

3.1 | Patient characteristics

Prior to transplantation, both recipient and donor were matched for blood group and human leukocyte antigen as closely as possible. For each recipient enrolled, an attempt was made to recruit their matched donor. However, in 21.4% (6/28) of recipients, a graft was received from an unrelated donor (through the national kidney exchange scheme or from an altruistic donor). Most recipients underwent preemptive transplantation (transplantation before initiation of maintenance dialysis), and the most common indication for renal transplantation was end-stage renal disease (10/28, 35.7%) due to underlying uncontrolled hypertension (5/10), diabetes mellitus (2/10), or immunoglobulin A nephropathy (3/10). A summary is provided in Table 1.

All patients received TP as per protocol outlined under the Methods section. Intraoperative intravenous UFH was administered to 7 (25%) recipients prior to clamping of the iliac vessels to prevent thrombosis in the recipient's iliac vein, with the dose administered being 3000 IU in 4 recipients, 2000 IU in 2 recipients, and 2500 IU in 1 patient. The median operation time in recipients was 126 minutes (IQR, 90-143).

Postoperative complications were observed in 5 recipients. Of them, 3 (10.7%) had delayed graft function; 1 (3.6%) had a hemoglobin

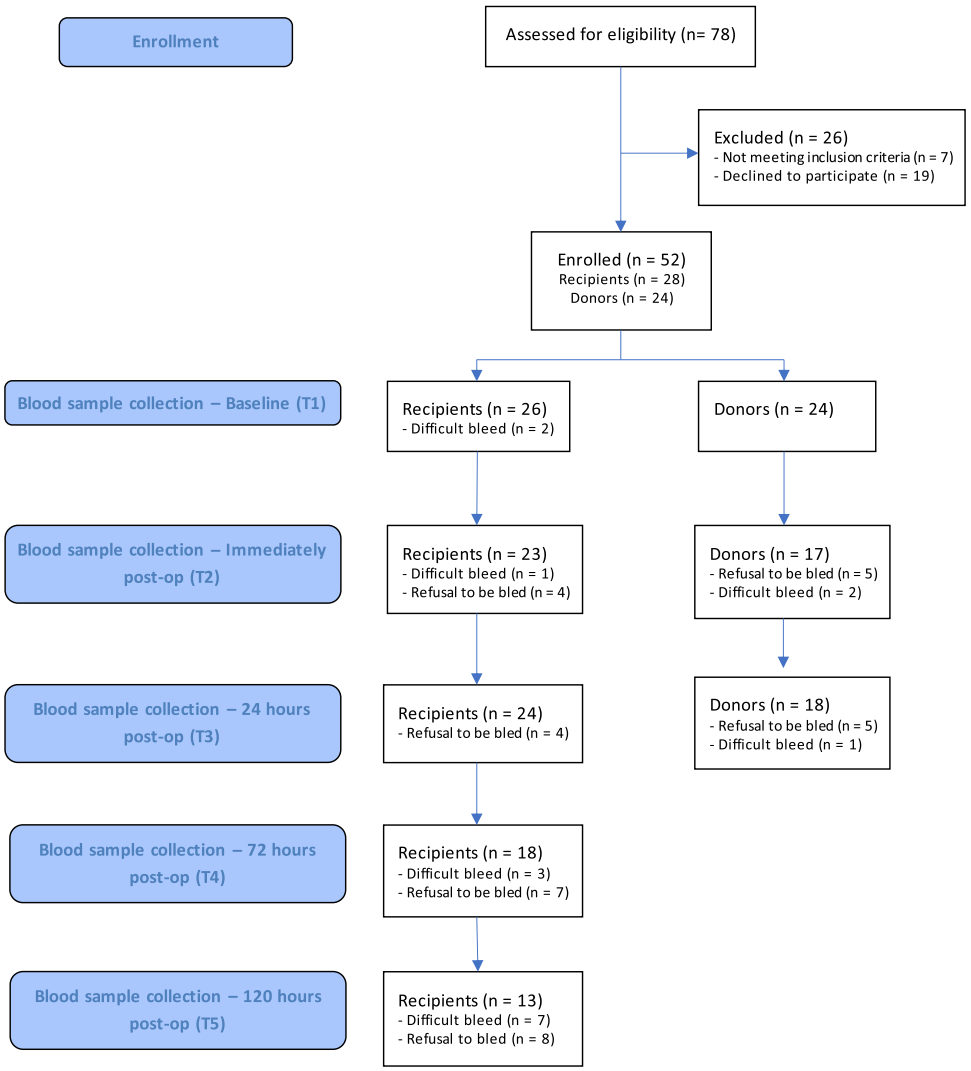

FIGURE Patient recruitment and progression through the study.

drop of >20 g/L, requiring red cell transfusion (2 units); and 1 (3.6%) had a nonfunctioning graft and had to resume maintenance dialysis (this patient had underlying focal segmental glomerulosclerosis, with persistence of disease assumed to be the reason for the nonfunctioning graft. No complications were reported in donors postoperatively. One recipient had a pulmonary embolism within 6 weeks of transplant surgery.

3.2 | Routine laboratory parameters at baseline in recipients and donors

As expected, compared with donors, median serum creatinine was significantly higher in recipients (median difference of 472 μmol/L; 95% CI, 426-544; $P < .0001$), while hemoglobin (median difference, 26 g/L; 95% CI, 21-36; $P < .0001$), platelet counts (median difference, 65 × 10^9/L; 95% CI, 30-91; $P = .003$), and albumin levels were significantly lower (median difference, 3 g/L; 95% CI, 1-6; $P = .008$). Supplementary Table S1 summarizes routine hematology and biochemistry parameters at baseline in recipients and donors.

3.3 | Hemostatic parameters at baseline in recipients and donors

At baseline, there was no significant difference in PT, APTT, fibrinogen, AT, TAT, PAI-1, and all TG parameters between donors and recipients (Supplementary Table S2).

Compared to donors, recipients had a significantly higher median level of FVIIIc (median difference, 41 IU/dL; 95% CI, 20-64; $P = .0003$), VWF (median difference, 55 IU/dL; 95% CI, 25-74; $P < .0001$), D-dimer (median difference, 0.10 mg/L fibrinogen equivalent units; 95% CI, 0-0.76; $P = .04$), and F1 + 2 (median difference, 165 pmol/L; 95% CI, 20-253; $P = .02$).

Although no significant differences were observed between recipient and donor groups at baseline, recipients had longer lag

TABLE 1 Summary of patient characteristics.

Characteristic	Recipients (n = 28)	Donors (n = 24)
Age (y), median (IQR)	41 (23-75)	48 (26-75)
Sex, n (%)		
Male	18 (64)	9 (38)
Ethnicity, n (%)		
White	16 (57)	14 (58)
Asian	9 (32)	8 (34)
Black	3 (11)	2 (8)
Cause of end-stage renal disease, n (%)		
End-stage renal disease (various causes[a])	10 (36)	
AD PKD	7 (25)	
FSGS	3 (10)	
Glomerulonephritis	1 (4)	
Other	7 (25)	
Pre-emptive transplant, n (%)		
Yes	15 (54)	
No	13 (46)	
Blood group, n (%)		
Group O	16 (57)	14 (58)
Non–group O	12 (43)	10 (42)
ABO incompatibility, n (%)		
No	24 (86)	
Yes	4 (14)	
Donor relationship, n (%)		
Unrelated	9 (32)	
Sibling	7 (25)	
Spouse	6 (21)	
Parent	3 (11)	
Offspring	3 (11)	
Graft received, n (%)		
Left kidney	18 (64)	
Right kidney	10 (36)	
Immunosuppression protocol, n (%)		
Baxilisimab/MMF/Pred/tacrolimus	28 (100)	
Surgical time (min), median (IQR)	126 (90-143)	117 (99-132)
Cold ischemia time (min), median (IQR)	227 (87-547)	
Intraoperative UFH, n (%)		
No	21 (75)	24 (100)
Yes	7 (25)	0
Dialysis, n (%)		0
Preoperative	13 (46)	
Postoperative	1 (4)	
Incidence of TE at 3 mo after transplant, n (%)	1 (4)	0

AD PKD, autosomal dominant polycystic kidney disease; FSGS, focal segmental glomerulosclerosis; MMF, mycophenolate mofetil; Pred, prednisolone; TE, thromboembolic event; UFH, unfractionated heparin.
[a]Uncontrolled hypertension, diabetes mellitus, and immunoglobulin A nephropathy.

time (median difference, 0.39 minutes; 95% CI, 0.11-0.67; P = .12) and higher peak height (median difference, 47 nM thrombin; 95% CI, 16-88; P = .18). Endogenous thrombin potential (ETP) was lower (median difference, 205 nM thrombin; 95% CI, 134-373; P = .27) and time to peak shorter (median difference, 0.7 minutes; 95% CI, 0.46-1.61; P = .35) in recipients compared to donors.

Group O was the most common blood group among both recipients and donors (57% and 58%, respectively). In donors, mean baseline VWF levels were significantly higher (P = .014) in those without group O (90 IU/dL; SD, 29 IU/dL) compared to those with group O (64 IU/dL; SD, 16 IU/dL). In contrast, VWF levels were not significantly different between recipients without group O and those with group O (130 IU/dL; SD, 51 IU/dL and 135 IU/dL; SD, 73 IU/dL, respectively, P = .838).

3.4 | Changes in routine hematology and biochemistry parameters over time in recipients

Compared to the baseline values, over time, there was a significant decrease in hemoglobin, platelets, creatinine, and albumin in recipients, although by day 5, there were signals that hemoglobin and platelet count were starting to rise in recipients (Supplementary Table S3).

3.5 | Changes in hemostatic parameters over time in recipients

Table 2 shows changes in routine coagulation and hemostatic variables in recipients from baseline (T1) up to T5. PT, APTT, and fibrinogen levels reduced over time, but only changes in APTT from T1 onward were significant. Significant increases were observed in FVIIIc, VWF, F1 + 2, D-dimer, and PAI-1 at all time points, while AT and TAT decreased.

For TG, lag time shortened from T1 to reach a nadir at T3 and T4 before recovering to baseline at T5. Mild increases were observed in ETP levels at T2 and T4. Peak height increased immediately after

TABLE 2 Changes in routine coagulation and hemostatic parameters over time in recipients.[a]

Parameter: reference range	Baseline (T1) n = 26	Immediately after operation (T2) n = 23	24 h after operation (T3) n = 24	72 h after operation (T4) n = 18	120 h after operation (T5) n = 13
Prothrombin time: NR, 8.8-11.7 s					
Absolute, median (IQR)	10.5 (10.1-10.9)	10.5 (10.3-10.9)	10.6 (10.4-11.1)	9.9 (9.8-10.5)	10.1 (9.9-10.3)
Change from baseline[b]		0 (P = .23)	+0.1 (P = .23)	−0.6 (P = .01)	−0.4 (P = .02)
Activated partial thromboplastin time: NR, 21-29 s					
Absolute, median (IQR)	25 (25-28.0)	23 (21-24)	23 (21-24)	22 (20-23)	23 (22-24)
Change from baseline[b]		−2 (P < .001)	−2 (P < .001)	−3 (P < .001)	−2 (P = .02)
Fibrinogen: NR, 1.8-3.5 g/L					
Absolute, median (IQR)	2.52 (2.1-2.6)	2.46 (2.2-2.6)	2.48 (2.3-2.6)	2.43 (2.18-2.58)	2.4 (2.15-2.53)
Changes from baseline		−0.06 (P = .56)	−0.04 (P = .74)	−0.09 (P = .41)	−0.12 (P = .83)
Factor VIIIc; NR 52-153 IU/dL					
Absolute, median (IQR)	117 (81-151)	195 (140-229)	172 (141-252)	168 (119-355)	302 (208-430)
Change from baseline[b]		+78 (P < .001)	+55 (P < .001)	+51 (P = .01)	+185 (P = .001)
von Willebrand factor: NR, 50-156 IU/dL					
Absolute, median (IQR)	123 (91-153)	242 (151-309)	183 (138-264)	211 (89-251)	266 (149-295)
Change from baseline[b]		+119 (P < .001)	+60 (P = .002)	+88 (P = .01)	+143 (P = .004)
Antithrombin: NR, 81-119 IU/dL					
Absolute, median (IQR)	92 (83-105)	82 (70-89)	78 (66-92)	88 (83-107)	109 (96-114)
Change from baseline[a]		−10 (P = .007)	−14 (P = .01)	−4 (P = .95)	+17 (P = .006)
Prothrombin fragments 1 + 2: NR, 91-137 pmol/L					
Absolute, median (IQR)	382 (195-522)	492 (435-802)	568 (467-922)	631 (522-765)	678 (518-933)
Change from baseline[b]		+110 (P = .001)	+186 (P = .002)	+249 (P = .001)	+296 (P = .006)
Thrombin-antithrombin complex: NR, <4.2 ng/mL					
Absolute, median (IQR)	7.3 (4.4-11.3)	3.1 (1.8-6.3)	4.0 (3.4-4.4)	8.8 (4.2-11.3)	5.6 (3.4-9.9)
Change from baseline[b]		−4.2 (P = .003)	−3.3 (P < .001)	+1.5 (P = .18)	−1.7 (P = .27)
D-dimer: NR, <0.44 mg/L FEU					
Absolute, median (IQR)	0.31 (0.19-1.35)	0.67 (0.35-1.27)	1.11 (0.75-3.93)	1.46 (0.85-2.27)	2.79 (1.60-4.60)
Change from baseline[b]		+0.36 (P = .11)	+0.8 (P = .006)	+1.15 (P = .01)	+2.48 (P = .01)
Plasminogen activator inhibitor-1 antigen: NR, 1-25 units					
Absolute, median (IQR)	12 (7-21)	23 (17-42)	22 (14-33)	24 (14-32)	27 (14-32)
Change from baseline[b]		+11 (P = .002)	+10 (P = .008)	+12 (P = .006)	+15 (P = .006)

(Continues)

TABLE 2 (Continued)

Parameter: reference range	Baseline (T1) n = 26	Immediately after operation (T2) n = 23	24 h after operation (T3) n = 24	72 h after operation (T4) n = 18	120 h after operation (T5) n = 13
Lag time: NR, 1.71-3.73 min					
Absolute, median (IQR)	3.83 (3.50-4.11)	3.50 (3.12-5.67)	3.0 (3.33-4.33)	3.00 (3.00-4.00)	3.64 (2.83-5.87)
Change from baseline[b]		−0.33 (P = .68)	−0.83 (P = .27)	−0.83 (P = .12)	−0.19 (P = .50)
Endogenous thrombin potential: NR, 1222-2754 nM hrombin					
Absolute, median (IQR)	1470 (1265-1843)	1521 (794-1789)	1461 (1348-1862)	1525 (1047-1744)	1438 (1117-1833)
Change from baseline[b]		+51 (P = .88)	−9 (P = .91)	+55 (P = .78)	−32 (P = .77)
Peak height: NR, 231-507 nM thrombin					
Absolute, median (IQR)	253 (200-293)	271 (131-355)	269 (243-354)	338 (147-410)	321 (224-394)
Change from baseline[b]		+18 (P = .88)	+16 (P = .18)	+85 (P = .09)	+68 (P = .09)
Time to peak: NR, 3.68-6.12 min					
Absolute, median (IQR)	7.33 (6.50-8.50)	6.50 (5.67-8.92)	6.50 (6.00-7.50)	6.67 (5.50-6.67)	6.34 (5.92-7.33)
Change from baseline[b]		−0.83 (P = .39)	−0.83 (P = .01)	−0.66 (P = .02)	−0.99 (P = .02)

FEU, fibrinogen equivalent units; NR, normal range.
[a]Patients with missing data points were excluded from the analyses.
[b]Median change from baseline calculated using the Wilcoxon rank test.

surgery, reaching a peak at T4. TTP shortened over time from T1, with significant differences from T1 seen at T3, T4, and T5.

3.6 | Changes in routine hematology and biochemistry parameters over time in donors

Compared with the baseline values, the median serum creatinine increased significantly over time, while eGFR decreased significantly, an expected change with the removal of a functioning kidney. There were significant decreases in hemoglobin, platelet count, and albumin, as shown in Supplementary Table S4.

3.7 | Changes in hemostatic parameters over time in donors

Both PT and APTT reduced significantly in the immediate post-operative period (T2) compared with the baseline values; however, at T3, there was no difference in these variables. No significant changes were seen in fibrinogen levels over time. Compared to baseline values, there was a significant increase in FVIIIc, VWF, F1 + 2, and D-dimer throughout the postoperative period. Although levels of antithrombin and TAT reduced from baseline to the postoperative period, these changes were not significant. PAI-1 levels did not change significantly. Significant changes were seen in peak height (median increase of 75, P = .005) and TTP (median decrease of 0.86, P = .02) from baseline up to T2 only, while changes in lag time and ETP were not significant (Table 3).

3.8 | Comparisons of laboratory result changes between recipients and donors

The mixed-model analysis showed significant differences in change between the 2 groups over time (T1-T3) for APTT (mean estimated difference, 3.5; 95% CI, 1.6-5.4; P < .0001), FVIIIc (mean estimated difference, 71.7; 95% CI, 41.4-102.0; P < .0001), VWF (mean

TABLE 3 Changes in routine coagulation and hemostatic parameters over time in recipients.

Parameter, reference range	Baseline (T1) n = 24	Immediately after operation (T2) n = 17	24 h after operation (T3) n = 18
Prothrombin time: NR, 8.8-11.7 s			
Absolute, median (IQR)	10.5 (10.2-10.7)	10.2 (10.1-10.4)	10.4 (10.1-11)
Change from baseline[a]		−0.3 (P = .04)	−0.1 (P = 1)
Activated partial thromboplastin time: NR, 21-29 s			
Absolute, median (IQR)	25 (24-28)	23 (22-25)	24 (22-26)
Change from baseline[a]		−2 (P = .002)	−1 (P = .15)
Fibrinogen: NR, 1.8-3.5 g/L			
Absolute, median (IQR)	2.2 (1.95-2.5)	2.1 (1.75-2.25)	2.2 (1.88-2.56)
Change from baseline[a]		−0.1 (P = .26)	0 (P = .74)
Factor VIIIc: NR, 52-153 IU/dL			
Absolute, median (IQR)	76 (47-80)	150 (125-193)	162 (134-224)
Change from baseline[a]		+74 (P = .001)	+86 (P < .001)
von Willebrand factor: NR, 50-156 IU/dL			
Absolute, median (IQR)	68 (57-91)	111 (83-137)	123 (103-171)
Change from baseline[a]		+43 (P = .004)	+55 (P = .001)
Antithrombin: NR, 81-119 IU/dL			
Absolute, median (IQR)	91 (82-107)	83 (73-90)	86 (75-93)
Change from baseline[a]		−8 (P = .36)	−5 (P = .49)
Prothrombin fragments 1 + 2: NR, 91-137 pmol/L			
Absolute, median (IQR)	217 (130-271)	562 (357-734)	392 (303-690)
Change from baseline[a]		+345 (P = .002)	+175 (P = .002)
Thrombin-antithrombin complex: NR, <4.2 ng/mL			
Absolute, median (IQR)	10.9 (5.9-11.3)	7.4 (3.9-10.8)	6.1 (3.9-11.1)
Changes from baseline		−3.5 (P = .11)	−4.8 (P = .15)
D-dimer: NR, <0.44 mg/L FEU			
Absolute, median (IQR)	0.21 (0.19-0.27)	1.43 (0.97-1.67)	1.60 (1.20-3.15)
Change from baseline[a]		+1.22 (P < .001)	+1.39 (P < .001)
Plasminogen activator inhibitor-1 antigen: NR, 1-25 units			
Absolute, median (IQR)	18 (11-25)	19 (16-30)	17 (15-27)
Change from baseline[a]		+1 (P = .46)	−1 (P = .43)
Lag time: NR, 1.71-3.73 min			
Absolute, median (IQR)	3.44 (3.16-4.01)	3.67 (2.92-4.33)	4.00 (3.33-4.78)
Change from baseline[a]		+0.23 (P = .38)	+0.56 (P = .08)
Endogenous thrombin potential: NR, 1222-2754 nM thrombin			
Absolute, median (IQR)	1675 (1468-1856)	1712 (1448-1849)	1563 (1308-1854)
Changes from baseline		+37 (P = .97)	−112 (P = .17)

(Continues)

TABLE 3 (Continued)

Parameter, reference range	Baseline (T1) n = 24	Immediately after operation (T2) n = 17	24 h after operation (T3) n = 18
Peak height: NR, 231-507 nM thrombin			
Absolute, median (IQR)	206 (171-273)	281 (266-292)	282 (201-318)
Change from baseline[a]		+75 (P = .005)	+76 (P = .33)
Time to peak: NR, 3.68-6.12 min			
Absolute, median (IQR)	8.03 (6.88-10.04)	7.17 (5.83-8.11)	7.49 (6.22-9.80)
Change from baseline[a]		−0.86 (P = .02)	−0.54 (P = .31)

FEU, fibrinogen equivalent units; NR, normal range.
[a]Median change from baseline calculated using the Wilcoxon rank test.

TABLE 4 Difference in thrombin generation parameters immediately after operation (T2) between recipients who received intraoperative unfractionated heparin and those who did not.[a]

Thrombin generation parameter	IO UFH	No UFH	Difference between means (±SEM)	P value
Lag time	5.29	3.80	1.5 (1.1)	.24
ETP	1209	1419	211 (477)	.68
Peak height	215.3	253	37.8 (99.1)	.72
TTP	9.2	7.4	1.8 (2.1)	.44

IO, intraoperative; UFH, unfractionated heparin; ETP, endogenous thrombin potential; TTP, time to peak.
[a]Unpaired t-test with Welch correction.

estimated difference, 88.7; 95% CI, 35.4-141.9; P = .001), F1 + 2 (mean estimated difference, 282.8; 95% CI, 143.9-421.8; P < .0001), TAT (mean estimated difference, 3.5; 95% CI, 1.9-5.1; P < .0001), D-dimer (mean estimated difference, 2.2; 95% CI, 1.0-3.3; P < .0001), PAI-1 (mean estimated difference, 9.2; 95% CI, 3.4-14.9; P = .002), and TTP (mean estimated difference, 1.5; 95% CI, 0.35-2.7; P = .01), as shown in Supplementary Figure S1.

3.9 | Impact of intraoperative UFH on TG (*in vitro*) in the immediate postoperative period in recipients

No recipient was on anticoagulants prior to transplantation. Seven (25%) recipients received a bolus of intravenous UFH intraoperatively; however, there was no significant difference in mean values for *in vitro* TG parameters at T2 between patients who received UFH intraoperatively vs those who did not (Table 4).

4 | DISCUSSION

Assessment of hemostatic changes before and immediately after surgery in renal transplant recipients (up to 5 days after surgery) and their donors (up to 24 hours after surgery) was evaluated over a 15-month period, with a total of 28 recipients and 24 donors enrolled at baseline.

At baseline, compared to donors, recipients had significantly higher median levels of FVIIIc, VWF, D-dimer, and F1 + 2, confirming the hypercoagulable status of patients with CKD due to ongoing inflammation [17,18]. Previous published studies comparing these variables between patients with CKD and healthy controls and adjusted for other risk factors such as hypertension, diabetes, and obesity [18,19] have shown similar results. However, interestingly, the greater degree of hypercoagulability in recipients with CKD was not identified by *in vitro* TG parameters at baseline. The likely explanation for this "lack of fit" between *in vivo* (F1 + 2 and D-dimer) and *in vitro* TG is that they measure different aspects of TG. F1 + 2 and D-dimer are markers that (directly or indirectly) quantify the amount of thrombin that has already been generated *in vivo* at a given time. In contrast, the *in vitro* TG test measures the potential of plasma to generate thrombin should coagulation-triggering circumstances arise. Further, although the TG test tries to "mimic" the *in vivo* TG process, it is crucial to recognize that other key cellular components, such as endothelium, red cells, white cells, and, in this study, platelets are missing.

After surgery, the pattern of hemostatic changes in recipients and donors was by and large similar for most assays, with FVIIIc, VWF, F1 + 2, D-dimer, and PAI-1 increasing from baseline and AT activity

and TAT reducing. A different pattern of change was seen for lag time (TG parameter), with recipients showing a steady decrease from baseline, while donors had a steady increase. There was no difference in direction of change for ETP and peak height between the 2 groups. Collectively, these changes show an overall prothrombotic tendency for both donor and recipients in the immediate postoperative period, and these results support guideline recommendations to administer TP after surgery in these individuals [20].

The mixed-model analysis showed that differences in changes between the 2 groups were more significant for APTT, VWF, FVIII, D-dimer, F1 + 2, TAT, PAI-1, and time to peak (for TG test), with the magnitude of changes being more pronounced for recipients. It is well known that many patient-related factors (eg, age, body weight, ABO antigen status, diet, smoking, ethnicity, and exercise) affect the levels of VWF and FVIII [21,22]. However, in this study, the significant elevation of both biomarkers is likely to have been due to chronic ongoing underlying inflammation, which is present in patients with CKD and still persistent in renal transplant recipients in the early posttransplant period [23,24]. Further, underlying endothelial damage due to chronic renal disease [25] and the use of immunosuppressive medications in these patients will result in endothelial cell activation with release of VWF. Endothelial damage can persist even up to 1 year after transplantation [26]. Increased levels of both FVIIIc and VWF have been shown to increase the risk of venous and arterial thrombosis [27,28], and these data, together with the results provided here, strengthen the argument for initiating pharmacologic TP in these patients.

F1 + 2 is formed during the generation of thrombin from prothrombin, while TAT levels demonstrate that thrombin has been formed and (subsequently) inhibited by AT. Accordingly, elevation of F1 + 2 and TAT markers reflects the occurrence of an *in vivo* TG process. D-dimer, on the other hand, is regarded as a marker of fibrin turnover and reflects *in vivo* TG as well as fibrin formation and lysis. The plasma half-life of F1 + 2, TAT, and D-dimer is 60 to 90 minutes, 15 minutes, and 6 to 8 hours, respectively [29,30]. In this study, F1 + 2 and D-dimer rose significantly over time in recipients, but TAT levels did not. The reason for the discrepancy in the pattern of change between F1 + 2 and TAT could be explained by the difference in the plasma half-lives between the 2, meaning that TAT is cleared quickly from the bloodstream by the liver [31]. There are no previous studies on changes in TAT in patients with renal transplants for comparison. Two studies looking at changes in TAT after elective total hip replacement (where patients received either subcutaneous heparin prophylaxis [32] or compressive elastic stockings [33] from the day before surgery up to discharge) showed the opposite: significant increases in TAT after surgery [32,33], with the highest levels seen immediately after the operation [33]. One study comparing F1 + 2 and TAT levels in patients with disseminated intravascular coagulation showed that levels were markedly elevated in patients with disseminated intravascular coagulation compared to those in controls, but plasma concentrations of TAT were much lower than those of F1 + 2 [34].

D-dimer increased throughout the postoperative period in recipients. As previously reported, the sustained elevation of D-dimer in recipients could reflect chronic renal-induced coagulopathy, which may require further time for resolution [14,35]. However, like the baseline values, the greater degree of hypercoagulability after surgery (ie, high F1 + 2 and D-dimer) was not evident in the *in vitro* TG test, and other studies have reported this discrepancy between F1 + 2, D-dimer, and *in vitro* TG test results [36,37]. Further, considering that VWF and FVIII levels were high after surgery in recipients, a higher level for ETP and peak thrombin results after surgery would be expected. However, previous studies have shown that the positive correlation between FVIII/VWF and TG parameters (particularly ETP and peak thrombin) is more pronounced when low TF (1 pM) is used for measuring *in vitro* TG (using a calibrated automated thrombinoscope) [38,39], and in this study, we used a higher TF concentration (5 pM) due to significant costs incurred with the use of low TF *in vitro* TG test. At higher TF concentrations, the sensitivity of this association is much lower [40].

Unlike in donors, PAI-1 activity increased significantly after surgery in recipients. PAI-1 is an acute phase protein and is increased in several inflammatory states, including CKD [41]. Postoperative fibrinolysis resistance (fibrinolytic shutdown) has been associated with a significant increase in PAI-1 after surgery. The high PAI-1 levels directly binding tissue plasminogen activator is the proposed mechanism [42,43]. Rat renal transplant models have shown upregulation and persistent expression of PAI-1, especially during chronic rejection, suggesting its role in chronic kidney loss [44]. At 6 months of follow-up, no recipient in this study had experienced chronic rejection. A repeat measurement at this time would have been useful to see if levels remained elevated.

No meaningful differences were noted in hemostatic parameters between recipients undergoing pre-emptive transplantation and those who were dialysis dependent. A larger study would be needed to confirm this finding.

No difference in TG was found between patients receiving a bolus of UFH intraoperatively compared to those who did not. This finding is likely because of the short half-life of UFH. A recent study by Nieuwenhuijs-Moeke et al. [45] questioned whether the use of intraoperative heparin is justified in patients with CKD undergoing renal transplant surgery. They compared the hemostatic profile using functional hemostatic tests and markers of *in vivo* activation of hemostasis between pre-emptively transplanted patients (in whom 5000-IU UFH bolus dose was administered during surgery), non–pre-emptively transplanted patients, and living donors and showed that the hemostatic state between pre-emptive and non–pre-emptive renal transplant recipients was comparable and that although the benefit of UFH was unclear, the distinction in UFH administration between the 2 groups was not justified.

This study has several limitations. One was the short follow-up duration for blood sample collection, confined by short inpatient stay for both donors and recipients. Previous studies with longer-term follow-up (ranging between 12 months to 14 years after

transplantation) have demonstrated endothelial injury, enhanced coagulation, and fibrinolytic system impairment after transplantation [46], whereas others have not [47]. The other limitations were incomplete follow-up sample collection for patient-related reasons (54% in recipients and 25% in donors); lack of evaluation of the role of platelets in overall hemostasis in these patients; d) the TF concentration used for *in vitro* TG test, as discussed above; e) lack of evaluation of the role of contact pathway system (through measurement of FXII and FXI activation); and f) small sample size (a larger study would be required to confirm the difference between the 2 groups).

5 | CONCLUSION

This study compared the effects of renal transplantation on prothrombotic, anticoagulant, and fibrinolytic markers, including TG, between recipients and their donors in the early postoperative period The results showed significant differences in hemostatic parameters between recipients and donors at baseline and in the early postoperative period, and although the initial patterns of change in the immediate postoperative period were similar, the persistence of a hypercoagulable state was notable in recipients despite recovery of renal function and initiation of TP. This is a relevant finding for transplant surgeons who tread a fine line between bleeding and thrombosis, and these data potentially support the clinical need for use of TP in the postoperative period in these patients. Larger studies are needed to confirm this observation.

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ETHICS STATEMENT

The study received approval by the local research ethics committee and Health Research Authority (Integrated Research Application System number 246513). Prior to enrollment, written informed consent was obtained from both recipients and donors.

AUTHOR CONTRIBUTIONS

R.K. collected the samples. R.K. and S.P. analyzed the samples. R.K. and J.T. performed the statistical analyses. All authors participated in the research design and writing of this paper.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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