Transplant International

ORIGINAL ARTICLE

Postoperative surgical-site hemorrhage after kidney transplantation: incidence, risk factors, and outcomes

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SUMMARY

Studies investigating the incidence, risk factors, and outcomes of surgical-site hemorrhage after kidney transplantation are limited. Patients who underwent a kidney transplant from 1 January 2000 to 30 September 2012 (followed until 31 December 2012) at Toronto General Hospital were included in this study. Postoperative surgical-site hemorrhage was defined as a drop in hemoglobin ≥20 g/l over a 24-hour period within 3 days of transplantation, followed by an ultrasound indicating a significant hematoma/collection. A total of 59 of 1203 (4.9%) kidney transplant recipients had postoperative surgical-site hemorrhage. Most cases (89.8%) occurred within 1 day after transplantation. Living donor transplants [OR 0.30 (95% CI: 0.16, 0.55)] and higher recipient BMI [OR 0.54 per 10 kg/m^2 increase in BMI (95% CI: 0.30, 0.99)] were associated with a significantly lower risk of bleeding. Chronic preoperative anticoagulant usage led to an increased risk of bleeding but was not statistically significant [OR 1.75 (95% CI: 0.52, 5.88)]. Postoperative hemorrhage was associated with a higher risk of graft loss or death [HR 1.62 (95% CI: 1.01, 2.60)]. While the incidence of postoperative surgical-site hemorrhage in kidney transplantation is relatively low, it may be associated with an increased risk of graft loss or death.

Transplant International 2017; 30: 474–483

Key words
incidence, kidney transplant, outcomes, risk factors, surgical-site hemorrhage

Received: 8 August 2016; Revision requested: 5 September 2016; Accepted: 18 January 2017; Published online: 2 March 2017

Introduction

While kidney transplantation is the treatment of choice for patients with end-stage renal disease [1], the surgical procedure is associated with potential complications. Postoperative surgical-site hemorrhage (SSH) may lead to compression of the kidney transplant, systemic sequelae of hemorrhagic shock, graft loss [2], and death [3]. Despite the potentially significant impact of bleeding events on clinical outcomes, studies investigating SSH after kidney transplantation are limited.

In most cases, SSH after kidney transplantation occurs in the early postoperative period and generally within the first few days after surgery [4]. Bleeding may occur from vascular anastomoses, vessels in the renal hilum which dilate following reperfusion, or retroperitoneal tissues surrounding the graft which were traumatized during exposure of the iliac fossa and mobilization of the iliac vessels. Bleeding is often captured late into the postoperative period (up to 2 weeks) [5], but few studies have focused on bleeds occurring within 24–48 h after kidney transplantation [2,6]. It is important

doi:10.1111/tri.12926

to distinguish early and late postoperative bleeds because the latter are not commonly due to the surgery but are instead characterized by distinct risk factors including biopsy procedures or therapeutic systemic anticoagulation [7].

The reported incidence of bleeding after kidney transplantation varies widely (0.2–14%) [2,5,6]. This is likely due to a number of factors including small or non representative populations used in previous studies, variation in the time period during which bleeds are captured and differences in the way in which bleeding was measured between studies. Most importantly, a clear operational measure to define clinically significant bleeding events has not yet been applied to the kidney transplant population. While hemoglobin (Hb) values [8–10], ultrasound reviews [2,11], and the need for transfusion [9,12] or re-operation [8,10,12–14] are often included in the definition, details such as the duration over which the Hb drops or the size of hematomas are not always reported. These details are necessary to gauge the severity and clinical significance of the bleeding event.

Although peri-operative anticoagulant therapy has been associated with an increased risk of bleeding [8,9], a thorough investigation of other potential risk factors for SSH has yet to be conducted in the kidney transplant population. Furthermore, the effect of postoperative SSH on long-term clinical outcomes including graft loss or death requires investigation. Therefore, the purpose of this study was to comprehensively assess the incidence, risk factors, and outcomes of SSH following kidney transplantation. In particular, we examine bleeding events occurring during the peri-operative period (within 3 days after kidney transplantation) using both Hb values and ultrasound reviews to identify all clinically relevant perigraft bleeds.

Materials and methods

Study design and participants

We conducted a single-center case–control study of patients receiving a kidney transplant from 1 January 2000 to 30 September 2012 (follow-up until 31 December 2012) at the Toronto General Hospital, Canada. Data for this study were obtained from the Comprehensive Renal Transplant Research Information System [15] and the Organ Transplant Tracking Record. Exclusion criteria included prior nonkidney transplants (including simultaneous multiorgan transplants), transplants performed at outside centers, age less than 18 years at the time of transplant, dual kidney transplants, prior kidney transplant, and patients with missing Hb values in the first 3 days post-transplant. Among the patients included in the final study cohort, those developing postoperative SSH were identified as cases (see definition below). Five controls were randomly selected from the remaining cohort for every case and were matched on the year of transplant. The cases and controls were then used in the subsequent risk factor and outcome analyses.

Case definition

The case definition for postoperative SSH was a drop in Hb ≥20 g/l [9,10] that occurred over a 24-hour period within 3 days after transplantation and a subsequent ultrasound (within 1 day prior to 2 days following the Hb drop) that had a hematoma or collection identified as large or with a volume ≥33.2 cm^3 (corresponding to a collection with a diameter of 4 cm in all dimensions, similar to methods previously used by Pawlicki *et al.* [11]). The volume was calculated using the formula for an ovoid (volume = ¾ π *abc*, where *a*, *b*, and *c* represented half of each of the three dimensions of the collection provided on the ultrasound). If multiple hematomas or collections were present, the sum of all volumes was taken.

Risk factors

A number of recipient, donor, transplant, and preoperative factors were assessed as potential risk factors for postoperative SSH. Recipient characteristics included age, sex, race, body mass index (BMI), diabetes mellitus, time on dialysis, and peak panel reactive antibody level. Donor factors included age, sex, BMI, donor type (deceased or living), donation after circulatory death (DCD), and expanded criteria donor (ECD). Transplant factors included the number of graft arteries, cold ischemia time (CIT), type of nephrectomy (open or laparoscopic), and year of transplant. Preoperative characteristics were also examined including chronic anticoagulant/antiplatelet therapy, preoperative platelet count, and preoperative international normalized ratio (INR).

Analytical methods

The incidence of postoperative SSH was calculated as the proportion of patients who experienced the event in the overall study cohort in the first 3 days after kidney

transplantation. Time to bleeding was defined as the date of transplant to the date when the Hb dropped at least 20 g/l. Potential risk factors were examined using univariable and multivariable conditional logistic regression models. Under the multivariable model, risk factors were selected using the backward stepwise selection procedure.

For the outcome analysis, cases of postoperative SSH were considered the exposure group of interest and their controls were deemed nonexposed. The time origin for this analysis was the date of bleeding diagnosis, and the outcome was all-cause graft loss (i.e., return to chronic dialysis, preemptive retransplant, or death with graft function). The Kaplan–Meier product–limit method was used to assess time to graft failure and/or death between patients who experienced postoperative hemorrhage and those that did not. The log-rank test was used to evaluate differences between survival curves. Univariable and multivariable Cox proportional hazards models were used to quantify the relative hazard for all-cause graft loss by SSH status.

Sensitivity analyses were performed to test the robustness of the main results. These analyses included the following: (i) forcing the following covariables into the statistical models: recipient age, recipient BMI, time on dialysis, and donor type and (ii) including duration of surgery (a surrogate for the complexity of the operation) as an additional variable in the model. The latter analysis was conducted on patients starting from 1 January 2003, as reliable data on duration of surgery were only available from this time point.

All statistical analyses were performed using STATA MP/4, version 12 (StataCorp, College Station, TX, USA www.stata.com). A two-sided $P < 0.05$ was considered statistically significant. The study was approved by the Research Ethics Board at Toronto General Hospital, University Health Network.

Results

A total of 1953 kidney transplant patients were eligible for this study. The following patients were excluded: 254 prior nonkidney transplant recipients (including simultaneous multi-organ transplants), 222 recipients transplanted outside of our center, 1 recipient under 18 years of age at the time of transplantation, 68 dual kidney transplants, 177 prior kidney transplant, and 28 patients with missing Hb values in the first 3 days post-transplant. This resulted in a final cohort of 1203 patients.

Incidence of postoperative SSH

Among the final cohort, 426 patients (35.4%) had a drop in Hb ≥20 g/l occurring over a 24-h period within 3 days post-transplant. A total of 405 of the 426 patients had a post-transplant kidney ultrasound within 3 days post-transplant. Nine of the remaining 11 patients had ultrasounds between 4 and 7 days post-transplant, 1 patient after 19 days, and 1 patient after a postoperative kidney transplant biopsy after 3 days post-transplant. Of these patients, 59 (4.9% of the total cohort) had an ultrasound confirming a significant bleed and were thus defined as the cases. The baseline characteristics of the cases and controls are shown in Table 1. A histogram of the time to bleeding after transplant is shown in Fig. 1. The majority of bleeding cases (89.8%) occurred within 1 day post-transplant. No bleeding events occurred at 3 days post-transplant.

Risk factors for postoperative SSH

Results of the univariable analysis of potential risk factors are shown in Table 2.

Every additional year on dialysis significantly increased the risk of bleeding by 13% [odds ratio (OR) 1.13 (95% CI: 1.06, 1.22), $P = 0.001$] and every 1-hour increase in CIT increased the risk by 9% [OR 1.09 (95% CI: 1.05, 1.12), $P < 0.001$]. ECD transplants almost doubled the risk of bleeding [OR 2.06 (95% CI: 1.16, 3.65), $P = 0.01$] while DCD transplants had no significant effect [OR 0.71 (95% CI: 0.22, 2.32), $P = 0.57$]. Living donor transplants were associated with a lower risk of bleeding with an unadjusted OR of 0.28 (95% CI: 0.16, 0.47), $P < 0.001$. Although chronic anticoagulant or antiplatelet therapy were both associated with an increased risk of postoperative SSH, these associations were not statistically significant [OR 1.75 (95% CI: 0.52, 5.88), $P = 0.36$ and OR 1.26 (95% CI: 0.70, 2.27), $P = 0.43$, respectively]. A summary of the preoperative anticoagulant and antiplatelet agents used among patients is provided in Table S1.

The backward stepwise selection procedure selected four key risk factors from the total pool of factors analyzed in the multivariable model (Table 3). Donor type had a strong effect on postoperative SSH as living donor kidney transplants had a lower risk of bleeding by 70% versus deceased donor kidney transplants [OR 0.30 (95% CI: 0.16, 0.55), $P < 0.001$]. Higher recipient BMI was also associated with a decreased risk for bleeding [OR 0.54 per 10 kg/m^2 increase in BMI (95% CI: 0.30, 0.99), $P = 0.04$].

Table 1. Baseline characteristics.

Characteristics	Number of patients $N = 354$	Measurements		
		Nonbleeding $n = 295$	Bleeding $n = 59$	P value
Recipient factors				
Age (years), mean ± SD	354	49.7 ± 13.7	49.2 ± 12.6	0.82
Sex (%)				
Male	212	61.0%	54.2%	0.35
Female	142	39.0%	45.8%	
Race (%)				
Not-white	122	35.3%	36.8%	0.84
White	221	64.7%	63.2%	
BMI (kg/m^2), mean ± SD	350	26.6 ± 5.6	25.2 ± 5.9	0.09
History of diabetes mellitus (%)				
Non-DM	262	73.7%	78.0%	0.36
DM	90	26.3%	22.0%	
Time on dialysis (years), median (IQR)	353	2.8 (0.9, 5.3)	3.9 (2.5, 6.2)	0.001
Peak PRA (%)				
=0%	198	57.1%	50.9%	0.32
>0%	155	42.9%	49.2%	
Donor factors				
Age (years), mean ± SD	351	45.9 ± 13.6	49.6 ± 12.5	0.06
Sex (%)				
Male	171	46.8%	58.6%	0.06
Female	180	53.2%	41.4%	
BMI (kg/m^2), mean ± SD	346	26.7 ± 4.9	27.9 ± 5.8	0.10
Donor type (%)				
Deceased	170	43.1%	72.9%	<0.001
Living	184	57.0%	27.1%	
Donors after cardiac death (DCD), (%)				
No	139	78.7%	90.7%	0.13
Yes	31	21.3%	9.3%	
Expanded Criteria Donors (ECD), (%)				
No	121	71.7%	69.8%	0.52
Yes	49	28.4%	30.2%	
Transplant factors				
Number of arteries (%)				
=1	298	84.6%	84.8%	0.99
>1	54	15.4%	15.3%	
Number of veins (%)				
=1	333	93.5%	100.0%	<0.001
>1	19	6.5%	0.0%	
Cold ischemic time* (h), mean ± SD	143	12.7 (8.2, 16.1)	12.5 (9.5, 17.4)	0.72
Type of nephrectomy performed (%)				
Open	307	86.0%	93.2%	0.08
Laparoscopic	45	14.0%	6.8%	
Duration of surgery (min), median (IQR)	300	137 (119, 155)	138 (115, 164)	0.99
Transplant era				
2000–2006	108	30.5%	30.5%	
2007–2009	132	37.3%	37.3%	
2010–2012	114	32.2%	32.2%	
Preoperative factors				
Anticoagulant/antiplatelet therapy				
None	243	69.8%	62.7%	0.35
Anticoagulants†	25	6.4%	10.2%	
Antiplatelets	86	23.7%	27.1%	

Table 1. Continued.

Characteristics	Number of patients $N = 354$	Measurements		
		Nonbleeding $n = 295$	Bleeding $n = 59$	*P* value
Preoperative platelets	346	222 (172, 274)	213 (164, 263)	0.37
Preoperative INR	346	1.02 (0.96, 1.07)	1.01 (0.96, 1.07)	0.34

SD, standard deviation; IQR, interquartile range.

*Deceased donor only.

†Four patients were also on antiplatelets.

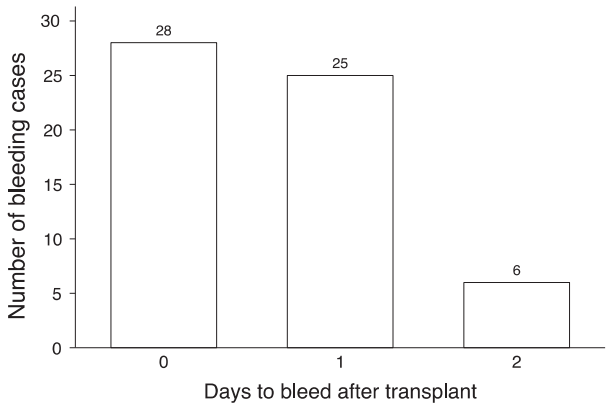

Figure 1 Histogram of the time to surgical-site hemorrhage diagnosis after kidney transplantation.

To assess the robustness of our primary findings, we conducted several sensitivity analyses. Forcing clinically relevant factors into the multivariable model (i.e., recipient age, recipient BMI, time on dialysis, and donor type) did not significantly change our results. Living donor transplants maintained a strong protective effect on bleeding [OR 0.30 (95% CI: 0.16, 0.58), $P < 0.001$] and higher recipient BMI continued to show a quantitatively lower risk of bleeding [OR 0.62 per 10 kg/m^2 increase in BMI (95% CI: 0.30, 1.26), $P = 0.19$]. When a forward variable selection procedure was used with the same *P* value cutoffs for entry (0.050) and removal (0.051) as the backward elimination procedure, the same model as the latter was chosen. A clinical

Table 2. Risk factors for postoperative surgical-site hemorrhage using a univariable conditional logistic regression model ($N = 354$, $n_{bleeding} = 59$).

Risk factor in model	Odds ratio (95% CI)	*P* value
Recipient age (per 10 year increase)	0.97 (0.77, 1.23)	0.82
Recipient sex (female versus male)	1.32 (0.73, 2.39)	0.35
Recipient race (White versus nonwhite)	0.95 (0.48, 1.90)	0.89
Recipient BMI (per 10 kg/m^2 increase)	0.60 (0.33, 1.09)	0.09
Time on dialysis pretransplant (per 1-year increase)	1.13 (1.06, 1.22)	0.001
Recipient history of diabetes (yes versus no)	0.79 (0.48, 1.30)	0.36
Recipient peak PRA (>0% vs. 0%)	1.31 (0.78, 2.19)	0.31
Donor age (per 10 year increase)	1.23 (0.99, 1.53)	0.06
Donor sex (female versus male)	0.62 (0.38, 1.02)	0.06
Donor type (living versus deceased)	0.28 (0.16, 0.47)	<0.001
Donor BMI (per 10 kg/m^2 increase)	1.56 (0.91, 2.66)	0.11
Donation after circulatory death (yes versus no)	0.71 (0.22, 2.32)	0.57
Expanded criteria donor (yes versus no)	2.06 (1.16, 3.65)	0.01
Number of arteries (>1 vs. 1)	0.99 (0.30, 3.28)	0.99
Cold ischemic time (per 1-hour increase)	1.09 (1.05, 1.12)	<0.001
Type of nephrectomy (laparoscopic versus open)	0.42 (0.16, 1.09)	0.07
Anticoagulant/antiplatelet therapy		
Anticoagulants versus none	1.75 (0.52, 5.88)	0.36
Antiplatelets versus none	1.26 (0.70, 2.27)	0.43
Initial platelets (every 10 unit increase)	0.98 (0.95, 1.02)	0.35
Initial international normalized ratio (INR) (per 10 unit increase)	1.72 (0.56, 5.26)	0.34

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Table 3. Risk factors for postoperative surgical-site hemorrhage using a multivariable conditional logistic regression model (N = 354, $n_{bleeding}$ = 59).

Risk factor in model*	Odds ratio (95% CI)†	*P* value
Donor type (living versus deceased)	0.30 (0.16, 0.55)	<0.001
Recipient BMI (per 10 kg/m^2 increase)	0.54 (0.30, 0.99)	0.04
Donor age (per 10 year increase)	1.19 (0.96, 1.48)	0.11
Donor sex (female versus male)	0.67 (0.38, 1.18)	0.16

*Backwards stepwise selection procedure used.

†Adjusted for all risk factors listed in the table. An odds ratio greater than 1 indicates an increased risk of bleeding while an odds ratio less than 1 represents a decreased risk of bleeding.

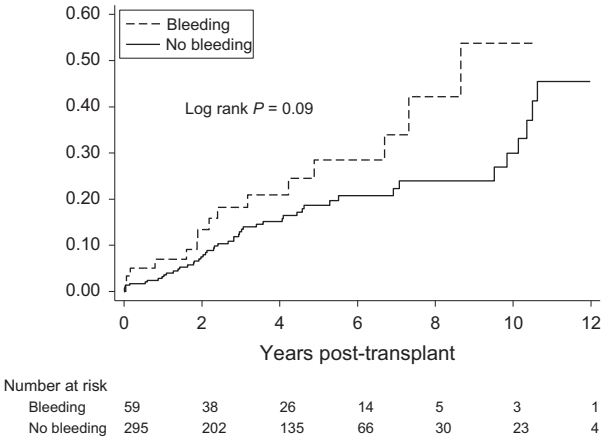

Figure 2 The cumulative probability of graft loss and/or death following kidney transplantation by postoperative surgical-site hemorrhage status.

judgment model that included recipient age, BMI, time on dialysis, donor type, expanded criteria donor status, cold ischemia time, and pretransplant anticoagulant use showed similar point estimates for donor type and BMI but with less statistical precision [OR 0.41 (95% CI: 0.15, 1.15) and OR 0.60 (95% CI: 0.29, 1.23), respectively]. Finally, the findings did not change when duration of surgery, a surrogate for the complexity of the operation, was included as an additional covariable in the model.

Outcomes of postoperative SSH

Among the 59 patients who experienced postoperative SSH, 28 (47.5%) were managed expectantly, 24 (40.7%) received red blood cell transfusions as the sole management for their bleed, and seven (11.9%) underwent re-operation for evacuation of the hematoma. The decision to undergo surgical revision was based on multiple factors including the presence of hemodynamic instability, decline in kidney function, and/or evidence of allograft perfusion abnormalities that would suggest impingement of blood vessels by an enlarging hematoma. Kaplan–Meier curves for graft loss or death stratified by bleeding status are shown in Fig. 2. The cumulative probability of graft loss and/or death was higher among bleeding patients compared to nonbleeding patients (log-rank P = 0.09). Table 4 shows that patients with (versus without) a postoperative SSH had a quantitatively higher risk of graft loss or death, with the final model showing a hazard ratio of 1.62 (95% CI: 1.01, 2.60), P = 0.04.

Table 4. Cox proportional hazards model for the effect of postoperative surgical-site hemorrhage on graft loss or death (N = 354, $n_{graft\ failure\ and/or\ death}$ = 64).

	Hazard ratio (95% CI)	*P* value
Model 1*	1.63 (0.99, 2.68)	0.06
Model 2†	1.61 (0.92, 2.81)	0.09
Model 3‡	1.62 (1.01, 2.60)	0.04

*Univariable model.

†Multivariable model using stepwise selection with forced variables: recipient age, recipient BMI, time on dialysis, donor type. Model stratified by preoperative INR (>1 or ≤1) and DCD transplant (Yes or No).

‡Multivariable model using stepwise selection. Model stratified by preoperative INR (>1 or ≤1).

When patients were stratified by the severity of bleeding, the cumulative probability of graft loss or death was highest in patients requiring transfusions or re-operation (Fig. S1). The univariable hazard ratio for transfusion or re-operation (versus no bleeding) was significantly elevated [HR 1.96 (95% CI: 1.02, 3.72); P = 0.04], while expectant management showed no significant increase [HR 1.31 (95% CI: 0.75, 2.27); P = 0.34]. Finally, when kidney transplant outcomes among patients with versus without bleeding were examined across donor type (Fig. S2), it was noted that the univariable hazard ratio associated with living donor kidney transplants was markedly elevated as compared to deceased donor kidney transplants [HR 4.28 (95% CI: 1.59, 11.51) vs. HR 0.84 (95% CI: 0.41, 1.71), P interaction = 0.02].

Discussion

To our knowledge, this is the largest study to date examining postoperative SSH after kidney transplantation. We used a comprehensive and detailed screening strategy that first captured any potential bleeding cases (indicated by a drop in Hb ≥20 g/l over a 24 h period within 3 days post-transplant) followed by a review of an ultrasound to confirm bleeding around the graft site. Furthermore, hematomas or collections meeting the *a priori* size criteria were selected as major bleeding events to exclude cases where dilution by large volumes of intravenous fluids in the peri- and/or postoperative periods may have contributed to a drop in Hb. Our rigorous screening procedure may explain the relative low incidence of postoperative SSH (4.9%), which is in the mid-range of previous estimates. Rates as low as 0.2–1.9% have been reported when only severe bleeds requiring re-operation were included [3,5,16]. Although the time period during which these severe bleeding events were captured ranged from 1 to 14 days, the rate is consistent with our finding that seven out of the 59 bleeding cases (11.9%) required re-operation representing an incidence of 0.6% in the total study population.

Hernandez *et al.* [2] reported a bleeding incidence of 14.7% where significant bleeds were detected using an ultrasound within 24 h along with the need for re-operation or transfusion. This report only focused on deceased donor kidney transplants. The highest incidence of bleeding ever reported is 25.4% where bleeding was determined by an ultrasound within 24 h of the transplant with a hematoma of diameter ≥4 cm [11]. The low size threshold for hematomas detected by ultrasound likely contributed to the high incidence estimate. Although center-specific variations in transplant populations may also contribute to the differences in reported bleeding rates, our study benefits from a large and diverse cohort. As a result, our reported incidence is likely an accurate reflection of the rate of significant postoperative SSH in the general kidney transplant population.

Most SSH events occur early in the postoperative period and generally within the first few days after operation [4]. In our study, we found that even within this period, the majority of events occurred 1 day after transplantation. Knowledge of this critical period for bleeding may aid in careful detection of significant bleeding in the postoperative recovery period. These results may also have important clinical implications for determining optimal timing of anticoagulation or antiplatelet re-administration. Many patients are systematically prescribed anticoagulation for a predisposition to thrombosis or following an incidence of stroke [17–19]. While these medications are usually stopped prior to surgery, the optimal time to re-initiate medication following transplantation is not clear. Our data suggest that the first 2 days post-transplantation is a high-risk period for the development of postoperative SSH and thus re-introduction of anticoagulants during this time should be avoided if possible.

Our study identified a few key risk factors for SSH after kidney transplantation. Donor type was found to have the strongest association with the risk of developing postoperative SSH. Both graft and recipient factors likely contribute to this finding. Differences in the techniques of graft procurement from living and deceased donors may play an important role. Careful hemostasis in the perinephric tissues is achieved during mobilization of the living donor kidney *in situ* prior to extraction, whereas deceased donor kidneys are usually procured en bloc with perinephric and retroperitoneal tissues. Moreover, the kidney is subsequently prepared for transplantation using cold sharp dissection on the back table where hemostasis from the perinephric and hilar tissues cannot be assessed until the time of reperfusion in the recipient. It is also possible that deceased donor transplants are more susceptible to bleeding due to supratherapeutic systemic anticoagulation administered to deceased donors prior to organ retrieval, or greater fragility of deceased donor tissues due to donor age, body habitus, and comorbidities. It is also important to note that deceased donor kidney transplant recipients have often waited much longer to receive a transplant compared to living donor kidney transplant recipients. The prolonged exposure to dialysis prior to transplant may increase bleeding risk due to its negative effects on tissue and vessel integrity.

Lower recipient BMI, longer CIT, and ECD transplants were found to be associated with the risk of postoperative SSH in univariable analysis. It is possible that these factors may have been selected for inclusion in the multivariable model if the sample size was larger. In many surgical procedures, high BMI is associated with an increased risk of complications including increased intraoperative and postoperative bleeding, decreased wound healing, and cardiac complications [20,21]. It is possible, however, that high BMI in the context of kidney transplantation may reflect the ability of increased tissue around the graft to effectively tamponade bleeding. Alternatively, it is possible that the increased technical difficulty of conducting ultrasounds in obese patients could reduce visualization of perirenal

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collections, but the superficial location of the allograft would likely make this less problematic in the transplanted kidney. Although the effects of CIT on bleeding from the kidney have not been studied, it is possible that endothelial cell injury reduces vessel integrity and thus increased susceptibility to bleeding. The relation between increased CIT on bleeding risk may also be a reflection of the effects of deceased donor kidneys on bleeding because these transplants generally have longer CITs. Kidneys from expanded criteria donors may have poorer vessel integrity and tissue quality. This factor may become important during the perioperative period, potentially increasing the susceptibility to bleeds from the anastomotic site or hilar tissues.

We found that patients on chronic preoperative anticoagulant or antiplatelet therapy had a quantitatively increased risk of postoperative SSH on univariable analysis, but the association was not statistically significant. Eng *et al.* [8] also found no effect of preoperative clopidogrel or warfarin usage on bleeding risk, but like our study, this may have been due to their relatively small number of bleeding events. Most patients in our cohort did not routinely receive prophylaxis for venous thromboembolism during the study period. While there are some data from previous studies to suggest that prophylactic anticoagulation may increase the risk of postoperative bleeding in kidney transplant recipients, these findings are limited by small cohorts and thus further investigation is warranted in a larger population [11].

Our study also showed that postoperative SSH after kidney transplantation is associated with an increased risk of long-term graft loss or death. Although the mechanism by which this may occur is not clear, it is possible that bleeding around the graft site early after transplantation may have a negative impact on long-term graft function by causing early graft dysfunction from mechanical compression or complications such as hypotension, anemia, need for blood transfusions, or sepsis from infected hematomas. Furthermore, significant hematomas requiring re-operation for evacuation may also be associated with worse long-term outcomes, as observed in our supplementary analysis by bleeding severity [5]. Patients at risk for postoperative SSH may have concomitant comorbidities and other unmeasured risk factors that may increase the risk of long-term graft loss or death. Finally, the univariable association between bleeding and long-term outcomes was more accentuated in living versus deceased donor kidney transplants. As a living donor kidney transplant is performed in a more controlled setting, significant bleeding may be a marker of patient factors that may portend a worse prognosis. However, this finding will require corroboration in a larger study with sufficient statistical power to allow for multivariable adjustment.

Despite the strengths of our study, there are some limitations that deserve note. First, although ultrasounds were used to confirm the presence of a perinephric hematoma in the setting of a Hb drop, some ultrasounds did not definitively indicate whether a large collection was in fact a hematoma. We reasoned that a collection meeting the specified size criteria in combination with a significant drop in Hb during the defined window presents a high probability of bleeding. Future work may include CT scans to confirm the identity of these collections, although these tests are not routinely done among patients at our center. While it is also possible that operator-dependent variations in ultrasounds may influence the results, all scans were conducted by certified technicians, using a standardized protocol, in one hospital-based imaging department, and where there are routine quality assurance measures in place to minimize variability. Second, our size criteria to include significantly large hematomas or collections as major bleeds was based in part on previous methods used by Pawlicki *et al.* [11]. This may have excluded some smaller collections that were clinically important. Future work may expand on our methods and include smaller hematomas that did not meet our size restriction. Third, given the narrow time window during which our study captured bleeding events, we were unable to accurately assess the effect of postoperative re-institution of anticoagulation or antiplatelet therapy on bleeding among patients who were chronically anticoagulated prior to transplantation. At our center, the standard practice for the postoperative re-institution of anticoagulant therapy is at 48–72 h for patients with standard indications for anticoagulation (e.g., atrial fibrillation, prior DVT, aortic valve replacement). Antiplatelet therapy is usually held until the time of discharge. Therefore, longer time frames to capture bleeding events will be necessary to determine the optimal timing of re-initiating anticoagulation post-transplant. Fourth, despite the large cohort, the relatively small number of SSH events limits the precision with which we can make inferences from the data. Finally, as with all observational studies, the potential for residual confounding (despite multivariable modeling) must be considered when interpreting our findings.

In summary, our study suggests that although the incidence of postoperative surgical-site hemorrhage in kidney transplantation is fairly low, it is associated with

an increased risk of graft loss and/or death. Deceased donor transplants may be the strongest predictor of surgical-site hemorrhage; however, lower recipient BMI may also be considered a significant risk factor. These findings can aid in identifying high-risk patients for postoperative hemorrhage to optimize their care during the perioperative period. Future studies are warranted to determine the underlying mechanisms by which postoperative hemorrhage in kidney transplant patients leads to worse long-term clinical outcomes.

Authorship

LDH and SJK: involved in study concept and design. LDH, AG, MS, OF, YL and SJK: involved in acquisition, analysis, or interpretation of data. LDH, OF and SJK: involved in drafting of the manuscript. LDH, AG, MS, OF, SJK: involved in critical revision of the manuscript for important intellectual content. YL and SJK: involved in statistical analysis. SJK: obtained funding. SJK: involved in administrative, technical, or material support. SJK: involved in study supervision.

Acknowledgements

The authors thank Dr. Gordon Tait for providing data on duration of surgery and red blood cell transfusions. The authors also thank the students of the Multi-Organ Transplant Student Research Training Program for collecting, entering, and auditing data for the Comprehensive Renal Transplant Research Information System (CoReTRIS) at the Toronto General Hospital, University Health Network.

Funding

No external funding was received to support this research.

Conflicts of interest

The authors declare that they have no conflicts of interest as it relates to this report.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Summary of pre-operative antiplatelet and anticoagulant agents among patients.

Figure S1. Kidney transplant outcomes by need for intervention or expectant management of post-operative surgical-site hemorrhage.

Figure S2. Post-operative surgical-site hemorrhage and kidney transplant outcomes by donor type.

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