The epidemiology of early deep vein thrombosis in kidney transplant recipients

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Background: Because kidney transplant recipients may be at increased risk for deep vein thrombosis (DVT) following transplantation, we investigated the incidence, risk factors, treatments and outcomes of early DVT among kidney transplant recipients.

Methods: An observational, single-centre cohort study was conducted among adult kidney transplant recipients from Jan. 1, 2005, to Dec. 31, 2016 with 1-year follow-up. Time to DVT was assessed using the Kaplan–Meier method. Cox proportional hazards and linear regression models were used to analyze risk factors for and outcomes of DVT.

Results: The cumulative incidence of DVT was 4.25% at 3 months after transplant. In multivariable analysis, the use of depleting induction agents (hazard ratio [HR] 2.13, 95% confidence interval [CI] 1.05–4.35]), white recipient race (HR 1.84. 95% CI 1.08–3.12), the use of kidneys from expanded criteria donors (HR 2.13, 95% CI 1.05–4.32) and lower recipient body mass index (HR 0.95, 95% CI 0.91–1.00) increased the risk for early DVT. Peritransplant DVT prophylaxis was not associated with early DVT. Early DVT was not associated with reduced graft function, death, graft failure or first hospital readmission.

Conclusion: Risk factors for early DVT in our cohort of kidney transplant recipients included white recipient race, use of depleting agents, lower recipient body mass index and use of expanded criteria donors. As practice patterns of donor and recipient selection in kidney transplantation evolve, the results of this study may aid in perioperative risk assessments and decision-making about the use of DVT prophylaxis.

Contexte : Étant donné que les receveurs de transplantation rénale peuvent être exposés à un risque accru de thrombose veineuse profonde (TVP) après l'intervention, nous avons voulu examiner l'incidence, les facteurs de risque, les traitements et l'issue de la TVP précoce chez les receveurs de transplantation rénale.

Méthodes : Nous avons procédé à une étude de cohorte observationnelle monocentrique auprès d'adultes ayant subi une transplantation rénale entre le 1er janvier 2005 et le 31 décembre 2016, suivis pendant 1 an. L'intervalle avant la TVP a été évalué par la méthode de Kaplan–Meier. Des modèles d'analyse à risques proportionnels de Cox et la régression linéaire ont servi pour l'analyse des facteurs de risque et l'issue de la TVP.

Résultats : L'incidence cumulative des TVP était de 4,25 % 3 mois après la transplantation. Dans l'analyse multivariée, l'utilisation d'agents d'induction antirejet (risque relatif [RR] 2,13, intervalle de confiance [IC] de 95 % 1,05–4,35]), des receveurs de race blanche (RR 1,84, IC de 95 % 1,08–3,12), l'utilisation de greffons rénaux provenant de donneurs à critères élargis (RR 2,13, IC de 95 % 1,05–4,32) et un indice de masse corporel (IMC) moindre chez les receveurs (RR 0,95, IC de 95 % 0,91–1,00) ont fait augmenter le risque de TVP précoce. La prophylaxie anti-TVP entourant l'intervention n'a pas été associée à la TVP précoce. La TVP précoce n'a pas été associée à une diminution du fonctionnement du greffon, au décès, à la défaillance du greffon, ni à la première réhospitalisation.

Conclusion : Dans notre cohorte de greffés du rein, les facteurs de risque de TVP précoce incluaient race blanche des receveurs, utilisation d'agents antirejet, IMC moindre des receveurs et donneurs à critères élargis. À mesure qu'évolueront les principes de sélection des donneurs et des receveurs pour la transplantation rénale, les résultats de cette étude pourraient aider à évaluer le risque péri-opératoire et à éclairer les prises de décision entourant la prophylaxie anti-TVP.

Kidney transplantation is the treatment of choice for end-stage renal disease, offering recipients improved survival and quality of life compared with dialysis. However, kidney transplant recipients (KTRs) are 7 to 8 times more likely to develop venous thromboembolism (VTE) than the general population, with the highest risk in the early post-transplant period.[1,2] Overall, the incidence of deep vein thrombosis (DVT) among KTRs ranges from 4.6% to 12.5%,[3–5] with most DVT events occurring within 3 months of transplantation.[2,4,5] VTE has been reported to have negative effects on graft function,[6] graft survival[2,7] and patient survival[2,8] in KTRs.

Risk factors for developing VTE include major surgery lasting more than 45 minutes, prior VTE, restricted mobility, age older than 40 years[9] and race.[8,10–15] Other risk factors reported include autosomal dominant polycystic kidney disease (ADPKD),[16] advanced chronic kidney disease[8] and cytomegalovirus infection.[17] To reduce the risk of VTE in KTRs, some have recommended routine perioperative mechanical prophylaxis such as compression stockings or prophylactic anticoagulation, or both.[4,18]

In recent years, practice patterns in kidney transplantation have changed, with the increasing use of higher risk kidney grafts from expanded criteria donors (ECDs).[19] Furthermore, transplantation is increasingly being offered to recipients at higher risk in terms of age, comorbidities and body mass index (BMI).

In this context, we undertook this study to investigate the epidemiology of VTE in the modern era by studying a large and diverse cohort of KTRs at a high-volume North American centre.

Methods

Study population and design

An observational single-centre cohort study was conducted among adult KTRs from Jan. 1, 2005, to Dec. 31, 2016, with a minimum follow-up of 1 year. Exclusion criteria were a prior nonkidney transplant, simultaneous multiorgan transplant, transplants outside our centre and no immunosuppressive induction therapy after transplantation. This study received approval from the Research Ethics Board of the University Health Network.

Data sources

DVT was defined as the partial or full occlusion of a vein in the deep venous system owing to a thrombus. Graft thromboses were excluded from this definition. Early DVT was defined as occurring within 3 months of transplant. Early DVT events were diagnosed by radiology, and data were collected through manual extraction from our centre's Organ Transplant Tracking Record by examining ultrasound diagnostic reports and progress notes. Variables collected were the date and anatomic location of early DVT events, treatments after the event and outcomes. Baseline characteristics, confounders and graft outcome data were obtained from the Comprehensive Renal Transplant Research Information System.[20] Data on DVT prophylaxis, defined as at least 1 dose of subcutaneous unfractionated heparin 5000 units administered between 24 hours before transplant and 48 hours after transplant, were collected from medication records in our centre's electronic patient record. Uncertain cases were adjudicated by clinical experts.

Risk factors and outcomes analysis

The risk factors for early DVT analyzed included recipient age at transplant, recipient race, recipient BMI, recipient history of cardiovascular disease (combined recipient history of coronary artery disease, peripheral vascular disease, congestive heart failure and stroke), years on dialysis before transplant, donor type, use of DVT prophylaxis, type of induction agent and transplant era.

DVT was also examined as an exposure variable in relation to clinical outcomes after transplant. Follow-up began 3 months after transplant and lasted for 1 year. Patients with primary graft nonfunction, graft failure, death or loss to follow-up within 3 months of transplant were excluded. Outcome variables were categorized into short-term and long-term outcomes. Short-term outcomes consisted of first hospital readmission after transplant, DVT and pulmonary embolus (PE). First hospital readmission was defined as the first overnight hospital stay after initial discharge after transplantation. DVT as an outcome had to present in a different anatomic location than the initial DVT event and had to be on or after the first DVT diagnosis date. PE was diagnosed by radiology and data were collected from patient medical records. The first early DVT diagnosis date was the origin for the analysis of short-term outcomes to ensure complete data capture. Short-term outcomes were evaluated up to 1 year after transplant.

Long-term outcomes included death-censored graft failure, death with graft function, total graft failure and graft function. Death-censored graft failure quantified graft failure events before death. Death with graft function quantified death events before graft failure. Total graft failure included both graft failure and death outcomes. Graft function was defined as the estimated glomerular filtration rate (eGFR) at 6 and 12 months after transplant. Three months after transplant was the origin for analysis of long-term outcomes. Patients with primary graft nonfunction after transplant, graft failure, death or loss to follow-up within 3 months of kidney transplant were excluded from the long-term outcome analysis. Long-term outcomes were evaluated up to Dec. 31, 2017.

Statistical analysis

The incidence of early DVT was calculated using the Kaplan–Meier product limit method. Patients were censored if they had graft loss, death or loss to follow-up within the 3-month post-transplant period. Incidence was reported as the number of events per 100 person-months. Anatomic locations and treatments of DVT events were analyzed descriptively. Risk factors for early DVT were analyzed using univariable and multivariable Cox proportional hazards regression models to calculate the hazard ratio (HR) with 95% confidence interval (CI). Cox proportional hazards models were also used to investigate outcomes of death-censored graft failure, death with graft function, total graft failure and first hospital readmission after DVT event. Cox proportional hazards models were fitted to analyze associations between DVT and post-transplant outcomes. Violations of the proportionality assumptions were checked using log(–log[S(t)]) plots and the interactions between the risk factors with time and Schoenfeld residuals (no significant departures from proportionality were detected). Kaplan–Meier curves stratified by early DVT were produced for each outcome. Linear regression was used to analyze eGFR at 6 and 12 months after transplant. Second DVT and PE events were analyzed descriptively owing to low occurrence. Missing values in the Cox proportional hazards models were imputed using multiple imputation. All statistical analyses were conducted using STATA, version 12.0.

Results

Study population

The total number of patients in this study was 1667 after we applied the exclusion criteria (Figure 1). Four of the excluded patients had DVT. Among the included patients, the mean recipient age at transplant was 51.4 (standard deviation [SD] 13.4) years. Sixty-one percent of the recipients were male, 61.2% were white and 46.4% had a living donor. Among those who had a deceased donor, 34.5% (308) had an ECD, while 65.5% (585) had a non-ECD. The transplant era 2005–2009 had the most recipients (37.3%). Table 1 summarizes the patients' baseline characteristics.

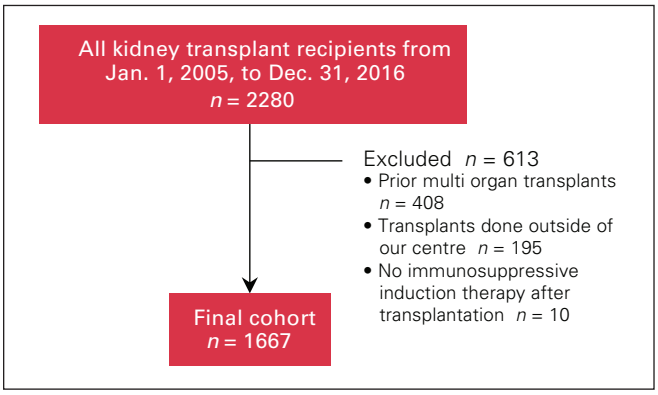

Fig. 1. Study population flow diagram.

Table 1: Baseline characteristics of recipients who experienced early deep vein thrombosis and their donors*

Risk factor	No. of patients	% of patients†
Recipient age at transplant, yr, mean ± SD	1667	51.4 ± 13.4
Recipient sex, male	1017	61.0
Recipient race		
White	900	61.2
Black or African Canadian	167	11.4
East Asian	190	12.9
South Asian	162	11.0
Indigenous	27	1.8
Pacific Islander	24	1.6
Recipient BMI, kg/cm^2, mean ± SD	1599	27.1 ± 5.6
Recipient history of diabetes mellitus	522	31.3
Recipient history of vascular disease‡	478	28.7
Time on dialysis before transplant, yr, median (IQR)	1667	3.3 (1.3–5.8)
Peak PRA		
0%	795	47.8
> 0%	870	52.3
Donor age at donation, yr, mean ± SD	1664	47.5 ± 14.5
Donor type		
Living	774	46.4
Deceased, ECD	308	18.5
Deceased, non-ECD	585	35.1
Delayed graft function		
Yes	360	21.6
Regraft		
Yes	182	10.9
Cold ischemic time, h (deceased donor only), median (IQR)	831	10.9 (7.9–14.8)
DVT prophylaxis		
Yes	849	50.9
Type of induction		
Nondepleting agent	415	24.9
Depleting agent	1252	75.1
Transplant era		
2005–2009	621	37.3
2010–2013	564	33.8
2014–2016	482	28.9

BMI = body mass index, DVT = deep vein prophylaxis; ECD = expanded criteria donor; IQR = interquartile range; PRA = panel reactive antibodies; SD = standard deviation.

*The origin is the transplant date, and the outcome variable is early DVT (DVT within 3 mo of transplant).

†Unless indicated otherwise.

‡Includes recipient history of coronary artery disease, recipient history of peripheral vascular disease, recipient history of congestive heart failure and recipient history of stroke.

Incidence of early DVT

During the 1-year follow-up, a total of 94 patients were diagnosed with DVT. Of those, 71 patients developed DVT within 3 months of kidney transplantation; the incidence was 4.2% and the incidence rate was 1.50 (95% CI 1.19–1.89) per 100 person-months (Figure 2). Most cases occurred in the lower limbs (28.4%), neck and chest (28.4%) and upper limbs (24.3%) (Table 2).

Potential risk factors for early DVT

Univariable analysis showed that older recipient age at transplant (HR 1.02, 95% CI 1.00–1.04]), longer time on dialysis (HR 1.09, 95% CI 1.02–1.15]), deceased ECDs versus living donors (HR 2.70, 95% CI 1.46–4.97), deceased non-ECDs versus living donors (HR 2.00, 95% CI 1.13–3.52) and induction type (depleting agent v. non-depleting agent) (HR 2.33, 95% CI 1.15–4.76) were significant risk factors for DVT. Figure 3 shows the cumulative probabilities of early DVT according to select risk factors. In the multivariable Cox model, only deceased ECDs (HR 2.13, 95% CI 1.05–4.32) and induction type (depleting agent v. non-depleting agent) (HR 2.13, 95% CI 1.05–4.35) remained significant risk factors. In addition, some variables that were not significant in the univariable analysis were found to be significant in the multivariable analysis, including white recipient race (HR 1.84, 95% CI 1.08–3.12) and recipient BMI (HR 0.95, 95% CI 0.91–1.00). Recipient history of vascular disease and administration of DVT prophylaxis were not found to be significant in either univariable (Appendix 1, Supplementary Table 1, available at www.canjsurg.ca/lookup/doi/10.1503/cjs.021821/tab-related-content) or multivariable analysis (Table 3).

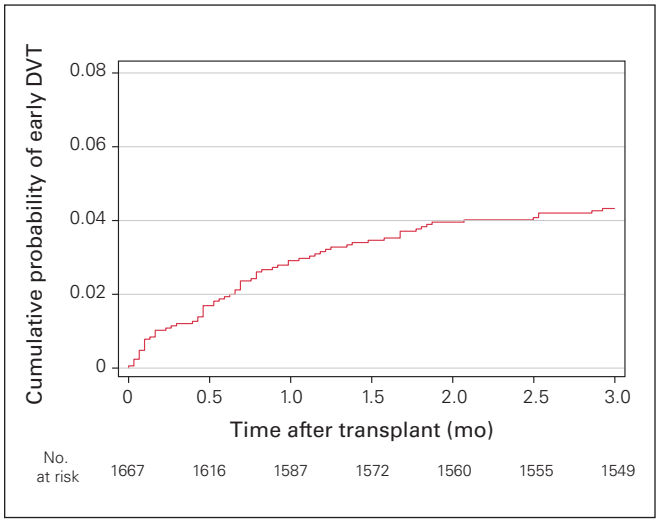

Fig. 2. Kaplan–Meier curve for early deep vein thrombosis (DVT) after kidney transplant.

Outcome analysis

Clinical outcomes were assessed in 1621 KTRs after the exclusion criteria were applied (Appendix 1, Supplementary Figure 1). The baseline characteristics of patients are presented in Appendix 1, Supplementary Table 2. We determined how many patients developed a second DVT or a PE event following an early initial DVT (< 3 mo after transplant) or a later initial DVT (3–12 mo after transplant). A total of 16.9% (12/71) of patients with an early DVT experienced a second episode, 11 of which were PE; while 21.7% (5/23) patients with a later DVT experienced a second event, including 3 PE events (Appendix 1, Supplementary Table 3). Owing to the low event number, there was insufficient power for a statistical comparison of these groups.

The incidence rates of clinical outcomes after transplant are shown in Appendix 1, Supplementary Table 4. No

Table 2: Location of first deep vein thrombotic events within 3 months after transplant

Location of DVT	No. (%) of DVTs
Upper limb	18 (24.3)
Lower limb	21 (28.4)
Neck and chest	21 (28.4)
Pelvis	4 (5.4)
Unspecified	10 (13.5)
Total	74* (100)

DVT = deep vein thrombosis.

*Some patients had more than 1 DVT location on the same DVT diagnosis date. Therefore, this number is greater than the number of patients (71) with a first DVT event within 3 months.

Table 3: Cox model for effect of risk factors on early deep vein thrombosis

	Multivariable analysis	
Risk factors	HR (95% CI)	*p* value
Recipient age at transplant (every 1-yr increase)	1.02 (1.00–1.04)	0.09
Recipient race (white v. non-white)	1.84 (1.08–3.12)	0.02
Recipient BMI (every 1 kg/cm^2 increase)	0.95 (0.91–1.00)	0.04
Recipient history of vascular disease* (yes v. no)	0.69 (0.39–1.19)	0.18
Time on dialysis before transplant (every 1-yr increase)	1.07 (0.99–1.15)	0.10
Donor type		
Deceased ECD v. living	2.13 (1.05–4.32)	0.04
Deceased non-ECD v. living	1.49 (0.78–2.87)	0.23
DVT prophylaxis (yes v. no)	0.76 (0.40–1.45)	0.41
Type of induction (non-depleting agent v. depleting agent)	0.47 (0.23–0.95)	0.04
Transplant era		
2010–2013 v. 2005–2009	1.31 (0.69–2.48)	0.41
2014–2016 v. 2005–2009	1.76 (0.79–3.93)	0.17

BMI = body mass index; CI = confidence interval; DVT = deep vein thrombosis; ECD = expanded criteria donor; HR = hazard ratio.

*Includes recipient history of coronary heart disease, recipient history of peripheral vascular disease, recipient history of congestive heart failure and recipient history of stroke.

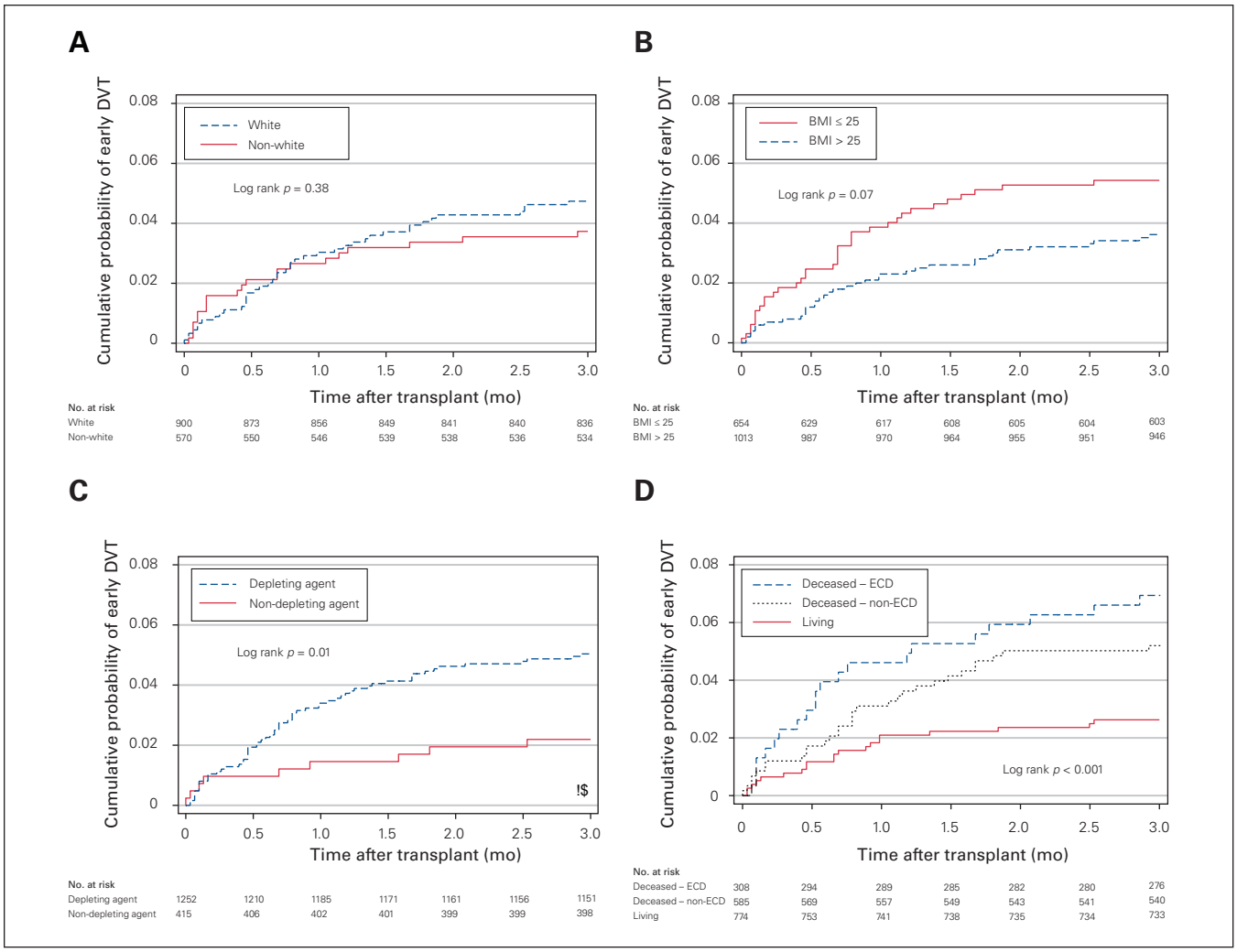

Fig. 3. Cumulative probability of early deep vein thrombosis (DVT) by (A) recipient race (white v. non-white), (B) recipient body mass index (BMI), (C) induction type and (D) donor type. ECD = expanded criteria donor.

short-term or long-term outcomes were found to be significantly associated with DVT (Appendix 1, Supplementary Figures 2 and 3), although death-censored graft failure approached significance in the multivariable Cox model (Appendix 1, Supplementary Table 5).

DVT treatments

Among the 71 patients with early DVT events, 90.1% (64/71) were medically treated. One (1.4%) was treated with surgery alone. Four (5.6%) received both medical and procedural therapies, while 2 (2.8%) did not receive any treatment before the end of the study follow-up or their DVT resolution.

Discussion

In this single-centre cohort study, we determined that the incidence of early DVT within 3 months after transplant in KTRs was 4.2%. Receipt of an organ from a deceased ECD, white recipient race and use of a depleting induction agent were found to significantly increase the risk of early DVT in the multivariable analysis. None of the studied outcomes, including first hospital readmission after transplant and graft-related outcomes, were significantly associated with early DVT in our cohort within the 1-year follow-up time frame.

The incidence of early DVT in our study was similar to values reported in the literature, which are between 4.6% and 6.6%.[4,21] In addition, a comparison between the incidence of DVT within 3 months of transplant and more than 3 months after transplant confirmed findings from previous studies, where the incidence of DVT peaked in the first 3–5 months and plateaued thereafter.[2,21] For example, during the 1-year follow-up, Kim and colleagues reported that 95% (57/60) of KTRs who developed DVT received the diagnosis within 3 months of transplant.[21] This is probably associated with the hypercoagulable state after kidney transplantation, which elevates the risk of thromboembolic events (TEs), particularly within 6 months of transplant.[22,23]

Compared with the use of non-depleting agents, the use of depleting agents in induction therapy was a significant transplant-related risk factor for early DVT in KTRs. Very few studies have examined the effect of induction therapies on developing DVT. For instance, Verhave and colleagues did not find induction therapy to be relevant to DVT, but they failed to compare KTRs who received depleting and non-depleting agents.[1] As depleting agents may be associated with thrombocytopenia[24] that should be protective against DVT, our findings suggest that alternate mechanisms initiated by depleting agents such as pro-inflammatory cytokine release or a greater dependence on central venous catheters for administration of these agents may contribute to the higher risk of DVT observed.

Donor- and recipient-related risk factors included deceased ECD, recipient age and race; age was significant in univariable but not multivariable analysis. Older age and receipt of an organ from a deceased donor have been found to be risk factors in other studies.[2,4] A possibility is that older recipient age and use of marginal kidneys result in a more complex postoperative course,[25,26] potentially including TEs such as DVT. Lower incidences of TEs have also been reported in patients who receive kidneys from living as opposed to deceased donors.[27] Additionally, our study found that white KTRs were more likely to develop early DVT than non-white KTRs. This result is in line with findings of many previous studies and may be related to white people having a higher chance of carrying subclinical factor V Leiden and prothrombin G20210A mutations that promote blood clotting; such mutations are rarely seen in Asian populations.[28–30]

The effect of DVT chemoprophylaxis using anticoagulants was assessed as a risk factor and was not significant in preventing DVT in our study. Inconsistent results were previously reported regarding DVT prophylaxis, with more studies reaching conclusions similar to those of our study that anticoagulants failed to reduce the number of DVT events.[1,18,31,32] Verhave and colleagues did not observe a decrease in DVT cases after a heparin prophylaxis protocol was implemented,[1] as was the case in our study, where no decrease in DVT was seen after the standard prophylaxis protocol came into effect in 2013. Conversely, Ubhi and colleagues reported 6 TEs in a group of patients without heparin treatment and none in the heparin-treated group.[33] The authors concluded that chemoprophylaxis was effective, although the results did not reach statistical significance. Most guidelines regarding DVT prophylaxis suggest that patients at a lower risk for TE should use compression stockings, and only those at moderate to high risk should be given chemoprophylaxis such as heparin.[1] Our results indicate that giving chemoprophylaxis to every KTR, regardless of their risk for TE, might not be effective in preventing early DVT.

Our study revealed a mild but significant association between lower BMI and increased risk of DVT. The small number of previous studies of DVT in KTRs have not revealed BMI as a risk factor.[1–3] The relationship between obesity and VTE is highly controversial in the literature, though many have observed an "obesity paradox" in patients with a variety of conditions including renal disease in which obesity confers a protective effect with respect to cardiovascular outcomes.[34] As the mean BMI of KTRs continues to increase over time commensurate with the trend in the general population, it is possible that our cohort of patients, with a wide BMI range in a relatively modern era, may be beginning to reveal similar protective effects of elevated BMI on some outcomes after kidney transplantation.

In our study, neither short- nor long-term outcomes were significantly related to early DVT. This was different from some studies that have reported a higher death rate and death-censored graft loss rate in patients with DVT.[2] However, Lam and colleagues studied VTE, including both DVT and PE;[2] because PE has been shown repeatedly to have a much higher mortality rate than DVT, it could contribute to the higher rate of adverse outcomes reported in their study. Furthermore, the short follow-up time of 1 year substantially limited the number of possible outcomes, especially long-term ones, that might truly be caused by DVT. Similar to our study, Ahn and colleagues had 1-year follow-up for the outcomes and did not find that DVT contributed to any outcomes.[4]

Limitations

Our study has a few limitations. Owing to the retrospective nature of the study, risk factors specific to DVT such as factor V Leiden and prothrombin G20210A mutations, antiphospholipid antibody syndrome and a history of prior unprovoked DVT were not recorded in the database and could not be assessed. Our database also lacked information about factors that may have contributed to upper-extremity DVT such as a history of dialysis, site of dialysis access and known central venous stenosis. We tried to compensate for this lack of information by combining different variables to obtain data on a previously reported risk factor. For example, recipient history of cardiovascular disease consisted of 4 variables (recipient history of coronary artery disease, peripheral vascular disease, congestive heart failure and stroke) in the original data set. Additionally, we excluded some risk factors found to be significant in previous studies such as African race and autosomal dominant polycystic kidney disease to save degrees of freedom to maintain a higher statistical power. To ensure that our risk factor analysis still captured the most important information, we kept risk factors that were either widely reported in the literature (e.g., recipient age and donor type), related to kidney transplantation but had been rarely studied (e.g., induction agent type) or were expected to affect DVT incidence

(e.g., DVT prophylaxis). Lastly, our study included only 1 year of post-transplant follow-up for the outcome of early DVT, so we were unable to fully capture and characterize the long-term outcomes such as death-censored graft failure that might be associated with early DVT in KTRs.

Conclusion

This large single-centre study of a cohort of KTRs demonstrated that the incidence of early DVT in our cohort was comparable to values reported in the literature. Risk factors included white race, use of a depleting agent, lower BMI and donation from ECDs. Early DVT was not clearly associated with patient or graft survival. As practice patterns of donor and recipient selection in kidney transplantation evolve, these results may aid in perioperative risk assessments and decision-making with regard to use of DVT prophylaxis.

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Contributors: O. Famure, J. Kim and A. Ghanekar conceived the study. M. Minkovich and I. Clotea acquired the data, which W. Qu, Y. Li, J. Lee and M. Selzner analyzed. W. Qu, M. Minkovich, I. Clotea and A. Ghanekar wrote the article, which O. Famure, Y. Li, J. Lee, M. Selzner and J. Kim critically revised. All authors agreed to be accountable for all aspects of the work.

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