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Original Article

D-dimer, Von Willibrand factor, and ADAMTS13 in renal transplant recipients

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Abstract

Introduction

Chronic kidney disease and renal transplants are associated with activation of coagulation. Microvascular thrombosis and fibrinolytic disorders have been recognized as main causes of allograft rejection in renal transplant recipients.

Aim

The aim was to evaluate D-dimer, Von Willibrand factor (VWF), and ADAMTS13 activity plasma levels in renal transplant recipients and investigate the association of these parameters and creatinine plasma levels, estimated glomerular filtration rate (eGFR), and time after transplantation.

Participants and methods

A total of 40 renal transplant recipients clinically stable at National Institute of Urology and Nephrology, 5–192 months after transplantation were enrolled in the study. Dimer, VWF, and ADAMTS13 activity levels were measured.

Results

We observed significant higher levels of ADAMTS13 ($P = 0.03$) in subgroup Cr3 (55.9%) with creatinine greater than 2.0 mg/dl as compared with Cr1 (43.3%) with creatinine less than 1.4 mg/dl and insignificant higher levels of D-dimer and VWF in subgroup Cr3 (566.22 ng/ml and 253.5 IU/dl, respectively) as compared with Cr1 (363.3 ng/ml and 240.6 IU/dl, respectively)**.** We observed also insignificant higher levels of D-dimer, VWF, and ADAMTS13 in subgroup with eGFR less than 60 ml/min/1.73 m^2 (478.6 ng/ml, 220.6 IU/dl, and 43.3%, respectively) as compared with eGFR greater than or equal to 60 ml/min/1.73 m^2 (322.73 ng/ml, 207.32 IU/dl, and 42%, respectively). There was a weak association between eGFR and D-dimer [odds ratio (OR)=−0.033, $P = 0.01$] and VWF (OR=−0.053, $P = 0.044$) and a weak association between creatinine plasma levels (>2.0 mg/dl) with D-Dimer (OR = 0.001, $P = 0.003$) and VWF (OR = 0.001, $P = 0.038$).

Conclusion

D-dimer, VWF, and ADAMTS were weakly associated with creatinine plasma levels and graft function. Other studies with a larger number of renal transplant recipients and from more than one center must clarify the role of hemostatic markers, especially, D-dimer, VWF, and ADAMTS13.

Keywords: ADAMTS13, D-Dimer, kidney function, Renal transplantation, Von willibrand factor

Introduction

Chronic kidney disease (CKD) and renal transplants are associated with activation of coagulation that favors a hypercoagulable state. Microvascular thrombosis and fibrinolytic disorders have been recognized as main causes of allograft rejection in renal transplant recipients, but the pathway through which it occurs has not been clarified yet [1].

D-dimer, Von Willibrand factor (VWF), and a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13 (ADAMTS13) have been suggested to evaluate the thrombotic status and rejection risk in renal transplant recipients [2].

D-dimer, a fibrin degradation product, is a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. Measurement of plasma D-dimer level has been shown as a

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useful diagnostic aid in suspecting deep vein thrombosis in medical patients [3]. Determination of D-dimer will improve the understanding of mechanisms linking kidney disease with venous thromboembolism and will allow a prevention effort [4].

VWF is an important component of the hemostatic system and a hypercoagulability state biomarker. It is a multimeric glycoprotein synthesized by endothelial cells and megakaryocytes. The synthesis occurs initially in the endoplasmic reticulum, where pre-VWF dimers are formed and migrate to the Golgi complex, where multimers are formed resulting in ultra-large multimers of the VWF exceeding 20 000 kDa (ULVWF). These multimers are stored in platelets and Weibel–Palade bodies of endothelial cells. VWF dimers are secreted into the plasma and the subendothelium, whereas the release of ULVWF is limited to sites of endothelial damage [5].

ADAMTS13, a circulating metalloprotease, was first cloned and identified as a member of a disintegrin and metalloprotease with thrombospondin type 1 repeats (ADAMTS) family in 2001. It is primarily synthesized in hepatic stellate cells [6], but is also found in other cells including endothelial cells, and megakaryocytes or platelets [7]. ADAMTS13 mRNA, which encodes the VWF-cleaving protease, has been detected in a variety of tissues, including the kidney. ADAMTS13 is secreted into plasma as an active enzyme at a plasma concentration of ~1 μg/ml [8]. In urine, ADAMTS13 has a molecular size similar to that in plasma, which indicates that the protease originates in the tubuli as such large proteins do not normally pass the glomerular filter [9]. It cleaves a large adhesive glycoprotein, VWF, which plays an essential role in primary hemostasis by recruiting platelets to the site of vessel injury. UL-VWF multimers can form high strength bonds with platelet GPIba and induce excessive platelet aggregation. This enzyme cleaves VWF in its A2 domain at a Tyr1605-Met1606 bond. Oxidation of Met1606, impairing ADAMTS-13 cleavage, results in the accumulation of UL-VWF polymers, which recruit and activate platelets more efficiently and bind more tightly to bacterial adhesions, thus contributing to the development of thrombotic and septic complications in CKD [10].

There is an association between ABO blood group and plasma VWF and coagulation factor VIII (FVIII) levels [11]. Non-O (A, B, or AB) individuals show increased risk of thromboembolism, whereas group O individuals have more pronounced inherited bleeding tendency and von Willebrand disease. The reason for this result is that ABO blood group determines VWF and FVIII levels [12]. Overall, 30% of plasma VWF levels depend on the effect of ABO group. Plasma VWF levels are approximately 25–30% lower in group O participants than in non-O individuals [13]. The proteolysis of VWF by ADAMTS13 is faster in group O participants than in non-O carriers [14].

Hemostatic biomarkers have been suggested to evaluate the thrombotic status and rejection risk in renal transplant recipients.

The aim of this study was to evaluate D-dimer, VWF, and ADAMTS13 activity plasma levels in renal transplant recipients and to investigate the association of these parameters with creatinine plasma levels, estimated glomerular filtration rate (eGFR), and time (months) after transplantation.

Participants and methods

Participants

A total of 40 renal transplant recipients clinically stable at the National Institute of Urology and Nephrology, 5–192 months after transplantation (median = 102), were enrolled in the study from November 2016 to May 2017. There were 29 (72.5%) male and 11 (27.5%) female patients, with age ranging from 21 to 61 years (median: 43 years). According to the general guidelines for renal transplantation, all recipients were under immunosuppression, consisting of the combination of corticosteroid and calcineurin inhibitor (tacrolimus or cyclosporine) [15]. We excluded recipients with acute rejection or under hemodialysis treatment at the time of study or had recent surgery, coagulopathies, thrombotic diseases, or acute infections.

Recipients were classified into two groups according to eGFR, determined by MDRD equation: eGFR greater than or equal to 60 ml/min/1.73 m^2 (N = 19) and eGFR less than 60 ml/min/1.73 m^2 (N = 21).

A second classification was done according to creatinine serum levels, into three groups as follows: Cr1, having recipients with creatinine less than 1.4 mg/dl (N = 19); Cr2, having recipients with creatinine within 1.4–2.0 mg/dl (N = 14); and Cr3, having recipients with creatinine greater than 2.0 mg/dl (N = 7). Moreover, a third classification according to the time (months) after transplantation include the following: T1: less than 24 months after transplant (N = 13), T2: 25–120 months (N = 8), and T3: greater than 120 months (N = 19).

The local ethics committee approved the study, and all recipients provided written informed consent for participation in the study.

Methods

Venous blood was collected in 5-ml tubes (3.8% sodium citrate) and centrifuged at 3000 rpm for 20 min at 4°C for D-dimer, VWF, and ADAMTS13. The plasma was separated and collected in aliquots stored at −20°C until assaying.

D-dimer and VWF antigen plasma levels were determined by enzyme-linked fluorescent assay, by VIDAS D-dimer Exclusion II and VIDAS VWF kits (BioMerieux SA, Lyon, France). ADAMTS13 was assessed by specific enzyme-linked immunoassay (ELISA) kit (Biobark, Optics Valley, Wuhan EIAab Sience Co., China). Intra-assay and interassay coefficients of variations were, respectively, 6.2 and 10% for D-dimer, 4.2 and 4.5% for VWF, and 5.3 and 9.6% for ADAMTS13.

Creatinine plasma levels were measured by specific enzymatic method (VITROS 5.1 FS). The estimated glomerular filtration rate was calculated using the abbreviated Modification of Diet in Renal Disease formula [eGFR-MDRDa: $175 \times \text{plasma creatinine (mg/dl)}^{-1,154} \times \text{age (years)}^{-0,203} \times 0.742$ (if female)×1.212 (if black)] [16].

Statistical analysis

Analysis of the data was performed using SPSS 21 for Windows (SPSS Inc., Chicago, Illinois, USA). Description of variables was presented as follows:

(1) Description of numerical variables was in the form of median and 25th and 75th percentiles.
(2) When comparing between two or more groups of independent variables Mann–Whitney *U*-test and Kruskal–Wallis tests were used. The difference was significant when *P* value was less than or equal to 0.05.
(3) For binary correlation, Spearman correlation test was used. The following points are the accepted guidelines for interpreting the correlation coefficient:
   (a) 0 indicates no linear relationship.
   (b) +1 and −1 indicate perfect positive and negative linear relationship, respectively.
   (c) Values between 0 and 0.3 (0 and −0.3) indicate no or a weak positive (negative) linear relationship.
   (d) Values between 0.3 and 0.7 (0.3 and −0.7) indicate a moderate positive (negative) linear relationship.
   (e) Values between 0.7 and 1.0 (−0.7 and −1.0) indicate a strong positive (negative) linear relationship.

To determine predictors for different outcome parameters, both univariate and multivariate regression analyses were performed.

Results

We measured D-dimer, VWF, and ADAMTS13 in 40 renal transplant recipients, classified according to eGFR (subgroups eGFR <60 ml/min/1.73 m^2 and eGFR ≥60 ml/min/1.73 m^2) and also according to creatinine plasma levels (subgroups Cr1, Cr2, and Cr3).

We observed significant higher levels of ADAMTS13 (*P* = 0.03) in group Cr3 (55.9%) with creatinine greater than 2.0 mg/dl as compared with Cr1 (43.3%) with creatinine less than 1.4 mg/dl (Fig. 1) and insignificant higher levels of D-dimer and VWF in group Cr3 (566.22 ng/ml and 253.5 IU/dl, respectively) with creatinine greater than 2.0 mg/dl as compared with Cr1 (363.3 ng/ml and 240.6 IU/dl, respectively) with creatinine less than 1.4 mg/dl (Figs. 2 and 3).

Moreover, there were insignificant higher levels of D-dimer, VWF, and ADAMTS13 in subgroup with eGFR less than 60 ml/min/1.73 m^2 (478.6 ng/ml, 220.6 IU/dl, and 43.3%, respectively) as compared with eGFR greater than or equal to 60 ml/min/1.73 m^2 (322.73 ng/ml, 207.32 IU/dl, and 42%, respectively) (*P* = 0.105, 0.915, and 0.915, respectively) (Figs. 4-6).

There were insignificant positive correlations between creatinine with D-dimer, VWF, and ADAMTS13 (*P* = 0.135, 0.478, and 0.382, respectively) and insignificant negative correlations between eGFR with D-dimer, VWF, and ADAMTS13 (*P* = 0.166, 0.329, and 0.281, respectively).

There were no differences in D-dimer, VWF, and ADAMTS13 levels in the three groups according to time after transplantation (T1, T2, and T3) (Figs. 7-9).

Preliminary analysis revealed a weak association between eGFR and D-dimer [odds ratio (OR)=−0.033, *P* = 0.01] and VWF (OR=−0.053, *P* = 0.044) (Table 1). Using multivariate analysis, we observed a weak association between D-dimer and eGFR less than 60 ml/min/1.73 m^2 (OR=−0.028, *P* = 0.032) (Table 2).

The univariate logistic regression showed a weak association between creatinine plasma levels (>2.0 mg/dl) with D-dimer (OR = 0.001, *P* = 0.003) and VWF (OR = 0.001, *P* = 0.038) (Table 3). Multivariate logistic regression analysis revealed that D-dimer (OR = 0.001, *P* = 0.013) was weakly associated with creatinine (Table 4).

Discussion

Assessment of renal function is essential for kidney transplant management. It has been a challenge to prevent early graft

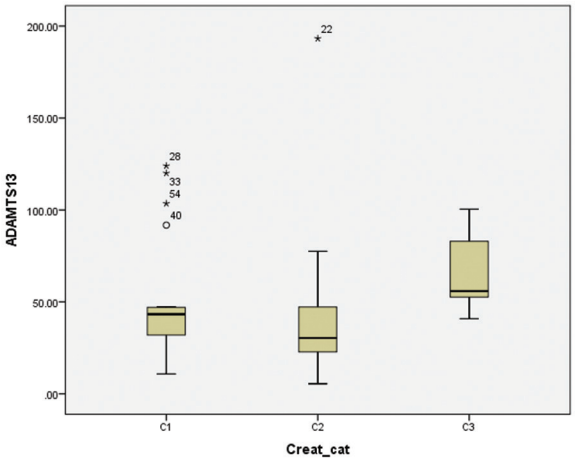

Figure 1: ADAMTS13% in groups of renal transplant recipients according to creatinine plasma levels. Data are presented as median+interquartile range.

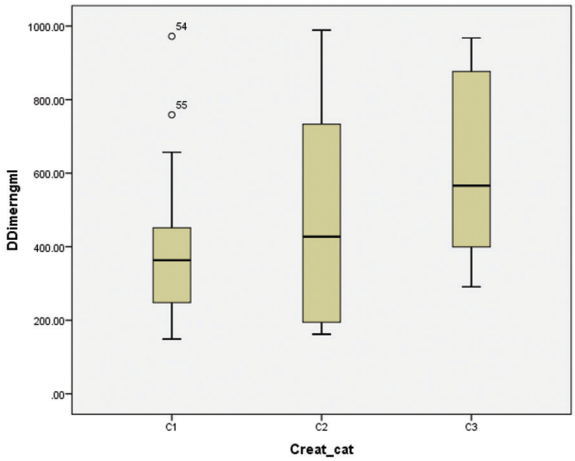

Figure 2: D-dimer in groups of renal transplant recipients according to creatinine plasma levels. Data are expressed as ng/ml and presented as median+interquartile range.

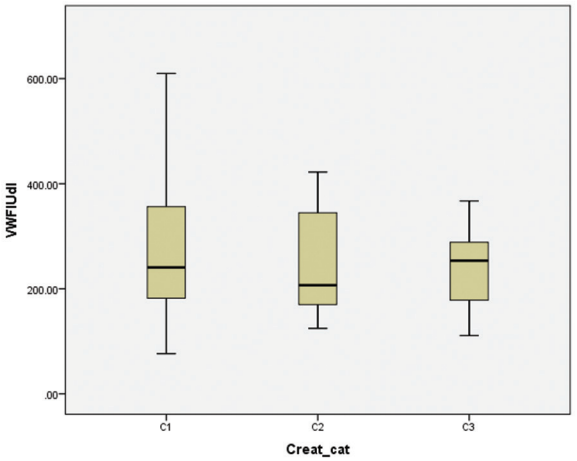

Figure 3: Von Willibrand factor in groups of renal transplant recipients according to creatinine plasma levels. Data are expressed as IU/dl and presented as median+interquartile range.

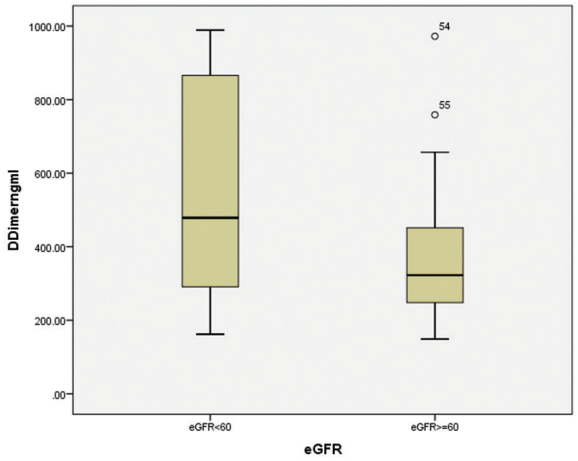

Figure 4: Plasma levels of D-dimer in groups of renal transplant recipients according to estimated glomerular filtration rate. Data are expressed as ng/ml and presented as median+interquartile range.

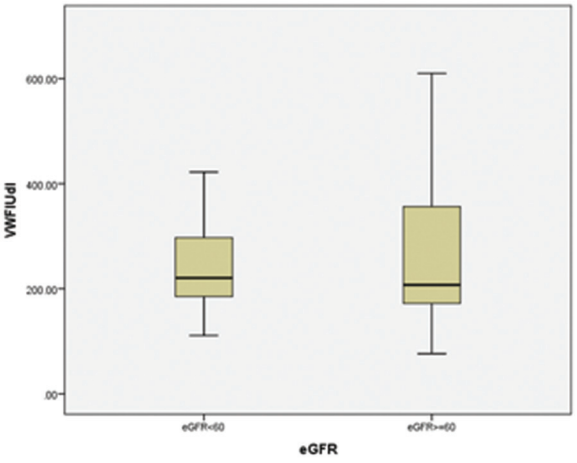

Figure 5: Plasma levels of Von Willibrand factor in groups of renal transplant recipients and according to estimated glomerular filtration rate. Data are expressed as IU/dl and presented as median+interquartile range.

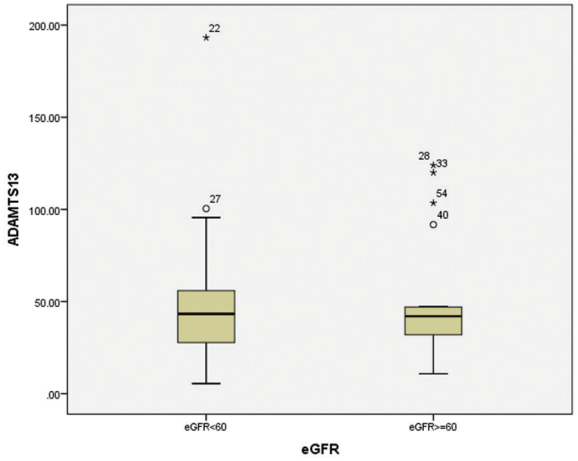

Figure 6: ADAMTS13% in groups of renal transplant recipients according to estimated glomerular filtration rate. Data are presented as median+interquartile range.

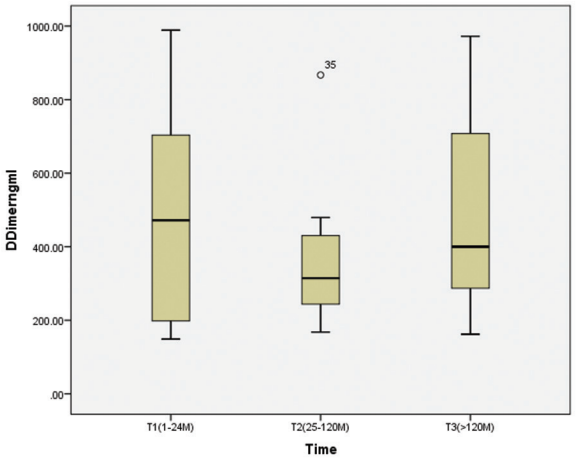

Figure 7: D-dimer in groups of renal transplant recipients according to time after transplantation. Data are expressed as ng/ml and presented as median+interquartile range.

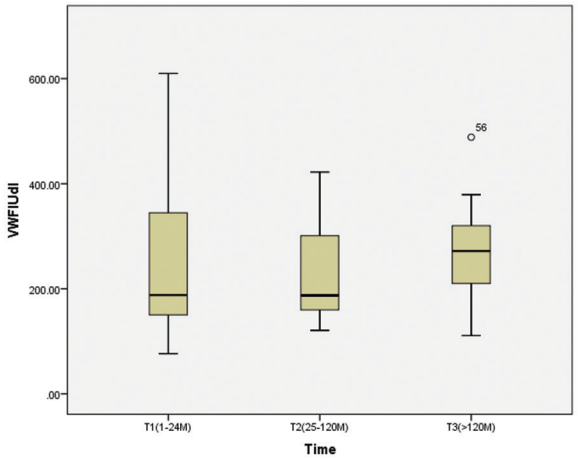

Figure 8: Von Willibrand factor in groups of renal transplant recipients according to time after transplantation. Data are expressed as IU/dl and presented as median+interquartile range.

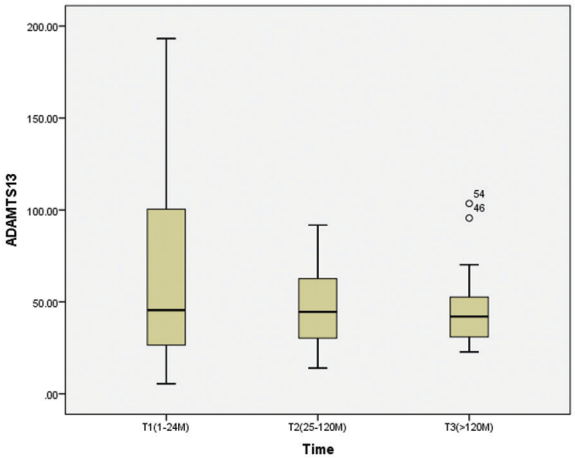

Figure 9: ADAMTS13% in subgroups of renal transplant recipients according to time after transplantation. Data are presented as median+interquartile range.

loss as the defective renal function is not detected until creatinine plasma levels have risen above baseline. Creatinine plasma levels are affected by many factors, such as muscle mass, sex, diet, liver function, medications, and time after transplant [17]. Because of the limitations of creatinine plasma levels to assess renal function, the eGFR was used in this study too. Kidney transplantation is considered a major surgical intervention, which can increase the risk of thromboembolic complications in recipients. Moreover, impaired fibrinolysis and impaired protein C activation are found after kidney transplantation [18]. Pawlicki *et al.* [19] study revealed that hypercoagulability in patients with CKD can be corrected after kidney transplantation.

Patients with advanced CKD usually have two conflicting hemostatic disorders: prothrombotic and hemorrhagic tendency. Thrombophilic factors is increased in patients with CKD. Shen *et al.* [20] observed an increase of VWF Ag levels and decrease in ADAMTS13 activity in patients with CKD. This indicates that CKD leads to a prothrombotic state. Uremia might be strongly associated with platelet dysfunction, which can increase the risk of hemorrhagic events in patients with ESRD. The pathogenesis of platelet dysfunction in renal failure is owing to defects in platelet-platelet (aggregation) and platelet-vessel wall (adhesion) interactions [21]. The study by Mohammed and Khalil [22] showed significant elevation of D-dimer, with higher level in females than males in their Sudanese patients with chronic renal failure.

The study by Domingueti *et al*. [23] has shown that increased plasma levels of VWF and reduced plasma levels of ADAMTS13 are associated with diabetic nephropathy and an increased risk of developing cardiovascular disease. The study by Domingueti *et al*. [24] stated that the increased D-dimer, VWF, and ADAMTS13 activity levels are associated with renal dysfunction in patients with type 1 diabetes, suggesting an association between endothelial dysfunction and hypercoagulability and nephropathy in type 1 diabetes.

Table 1: Univariate logistic regression in function of estimated glomerular filtration rate

Variables	eGFR <60 ml/min/1.73 m²		
	OR	CI	*P*
D-dimer	−0.033	−0.057 to −0.008	0.01
VWF	−0.053	−0.105 to −0.002	0.044
ADAMTS13	0.106	−0.042 to −0.008	0.255

CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; VWF, Von Willibrand factor.

Table 2: Multivariate logistic regression in function of estimated glomerular filtration rate

Variables	eGFR <60 ml/min/1.73 m²		
	OR	CI	*P*
D-dimer	−0.028	−0.054 to −0.003	0.032
VWF	−0.026	−0.086 to 0.033	0.380
ADAMTS13	0.058	−0.105 to −0.220	0.481

CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; VWF, Von Willibrand factor.

Table 3: Univariate logistic regression in function of creatinine plasma levels

Variables	Creatinine		
	OR	CI	*P*
D-dimer	0.001	0.000 to 0.001	0.003
VWF	0.001	0.000 to 0.003	0.038
ADAMTS13	−0.002	−0.006 to 0.001	0.173

CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; VWF, Von Willibrand factor.

Table 4: Multivariate logistic regression in the function of creatinine plasma levels

Variables	Creatinine		
	OR	CI	*P*
D-dimer	0.001	0.000 to 0.001	0.013
VWF	0.001	−0.001 to 0.002	0.371
ADAMTS13	−0.001	−0.005 to 0.003	0.520

CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; VWF, Von Willibrand factor.

Domingueti *et al*. [25] found that these parameters were elevated in diabetic patients with retinopathy compared with those without this complication. Cohen-Hagai *et al.* [26] found that diabetic patients on chronic HD had elevated VWF levels and activity with no significant change in ADAMTS13 activity. This conflict may be owing to the use of different assays and possibility of an in-vivo interaction preventing the cleavage of VWF multimers by ADAMTS13 [27].

Verhave *et al.* [28] found that the risk of thromboembolic events in kidney transplant recipients was eightfold higher than in the general population but not fully explained by the increased risk associated with hospitalization. Their results

show the important risk of thrombosis in patients who received a kidney transplant.

This study showed higher D-dimer plasma levels in group Cr3 as compared with Cr1, and in group eGFR less than 60 ml/min/1.73 m^2 as compared with eGFR greater than or equal to 60 ml/min/1.73 m^2 owing to reduction of urinary clearance and lower eGFR. This leads to a thrombotic or hypofibrinolytic state. In agreement with our study, Adams *et al.* [1] and Zbroch *et al.* [29] demonstrated endothelial injury, enhanced coagulation, and fibrinolytic system impairment, in long-term post-transplant. Antithymocyte globulins (ATG) treatment resulted in thrombocytopenia and increased plasma levels of D-dimer. Cumpelik *et al*. [30] found that binding of ATG to platelets causes platelet aggregation, α-granule release, membrane phosphatidylserine exposure, and the rapid release of procoagulant platelet microvesicles. ATG also activated platelets via binding to the low-affinity Fc gamma receptor. In contrary to our results, the study by Lezaic *et al.* [17] found an increase in D-dimer plasma levels in the short term after transplantation and could be corrected after a successful transplant. Cho *et al.* [31] showed that kidney transplant might correct the hypercoagulability of patients with CKD via improving renal function, because impaired renal function can be considered a primary etiology of the prothrombotic tendency in patients with CKD. The increase in D-dimer after kidney transplant may be a nonsignificant finding that could occur after any major operation, because D-dimer first increases at first seventh day after operation and then tends to decrease.

Our data showed higher VWF plasma levels in group Cr3 as compared with Cr1, and in group eGFR less than 60 ml/min/1.73 m^2 as compared with patients with eGFR greater than or equal to 60. Dubin *et al.* [32] agreed with our data, as they observed that the increased levels of VWF in renal transplant recipients with stable function are associated with worsening renal function. Pawlicki *et al.* [33] found higher VWF activity and D-dimer concentrations in 67 renal transplant recipients early after transplantation. However, Mota *et al.* [34] found no difference in VWF levels between groups according to creatinine plasma levels and were within the reference range. Moreover, they observed higher levels of VWF in patients with eGFR greater than or equal to 60 ml/min/1.73 m^2 as compared with patients with eGFR less than 60 owing to lower ADAMTS13 levels. Their recipients used immunosuppressive drugs that improve endothelial function and may cause maintenance of the VWF within the reference range [35].

This study showed that ADAMTS13 activity is significantly higher in group Cr3 as compared with Cr1. This may be owing to the facts that in patients with high creatinine levels, the renal filtration capacity is compromised, which could lead to lower ADAMTS13 clearance.

ADAMTS13 is insignificantly higher in the group with eGFR less than ml/min/1.73 m^2 as compared with the group with eGFR greater than or equal to 60 ml/min/1.73 m^2 but below the reference values. ADAMTS13 regulates the size and the activity of VWF multimers through rapid cleavage after release from endothelial cells. Decrease of ADAMTS13 and deficient VWF cleavage allow accumulation of ULVWF in the circulation and lead to thrombus formation [35].

The observation by Javaid and Quigg [36] agreed with ours. They found a decrease in ADAMTS13. They explained this by using immunosuppressive and steroids after transplantation which may interfere with circulating levels of immune and inflammatory mediators. In contrary to this study, Rios *et al*. [37] found elevation of ADAMTS13 activity even under aggressive immunosuppression, following renal transplantation, suggesting a role of kidney in ADAMTS13 level maintenance.

In summary, D-dimer, VWF, and ADAMTS13 are weakly associated with creatinine plasma levels and graft function. These data do not allow us to define which hemostatic marker should be measured during the follow-up of renal transplant recipients. Other studies with a larger number of patients and from more than one center must be performed to clarify the role of hemostatic markers, especially, D-dimer, VWF, and ADAMTS13.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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