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Plasma level of ADAMTS-13 in maintenance hemodialysis patients and its relation to arteriovenous fistula thrombosis

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Abstract

Background: End-stage renal disease is the final stage of chronic kidney disease in which irreversible deterioration in renal function occur and the body fails to maintain fluid and electrolyte balance, this need regular hemodialysis (HD) a process that removes accumulated solute from a patient with near-total renal function loss. Arteriovenous fistula (AVF) is the vascular access of choice for patients who require hemodialysis. AVF thrombosis is a major issue in hemodialysis patients, which increase their morbidity and lessen HD efficiency.

Objective: To assess plasma level of ADAMTS-13 in HD patients and its association with AVF thrombosis, and to correlate the plasma level of ADAMTS-13 with age, duration of dialysis, certain hematological parameters and estimated GFR.

Patients and Methods: This Cross_sectional study done on 60 patients with ESRD on regular HD sessions, 20 healthy persons were included as a control . The patients subdivided into two subgroups with and without AVF thrombosis. Plasma samples were freezed until the test for the level of ADAMTS-13 was done.

Results: The plasma ADAMTS-13 level was significantly lower in HD patients compared to control group ($P < 0.001$), and was a significantly lower in patients with a history of AVF thrombosis than HD patients without a history of AVF thrombosis. HD patients with AVF thrombosis had significantly lower eGFR compared to patients without a history of AVF thrombosis. There was a positive correlation of plasma ADAMTS-13 level with the mean of **eGFR** , platelet count and negative correlation with MPV.

Conclusion: Significant differences between HD patients and control regarding eGFR and hematological parameters . Plasma ADAMTS-13 level was significantly lower in patients compared to controls and significantly lower in patients group with AVF thrombosis than HD group without thrombosis.

Keywords: ADAMTS-13, Arteriovenous fistula, Hemodialysis, Thrombosis

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Introduction

Chronic kidney disease is defined as an abnormalities of kidney structure and function, presents for more than 3 months, with implications for health [1], the

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prevalence of major risk factors for CKD, including hypertension, diabetes, and obesity is high and increasing with both, the increase in population aging and decline in mortality from communicable diseases [2]. International differences in prevalence and incidence rates can be explained by many mechanisms, including economic differences, cultural values, and medical knowledge among at-risk populations [3]. Hemodialysis is a medical procedure applied for the management of uremia, [4] which result in a complex coagulation abnormalities occur and a variety of coagulation abnormalities contribute to an increased thrombotic tendency [5]. AVF is recommended as a first-line access [6]. Thrombotic episodes are mainly related to a reduction in vascular access blood flow which favors hypercoagulability [7]. The thrombotic tendency is a cause of complications in HD patients, with many fatalities. AVF thrombosis is the reason of 17–25% of cases of hospitalization [8]. In patients with ESRD, there are risk of both bleeding and venous thromboembolism [9]. A Disintegrin and Metalloprotease with Thrombospondin 13 (ADAMTS-13) is a proteolytic enzyme present on endothelial cells and platelets , it circulates in plasma at a concentration of 0.5-1 mg/L, it has a plasma half-life of 2 to 3 days [10,11]. Its substrate is VWF which plays a critical role in hemostasis by mediating platelet adhesion to injured vessels. Mutations affect the ADAMTS-13 gene or presence of autoantibodies to ADAMTS-13 lead to unrestricted formation of VWF that directly contributes to thrombus formation [12]. Patients with CKD have markedly lower levels of ADAMTS-13 activity and independently associated with steeper decline in kidney function [13].

The aim is to assess plasma level of ADAMTS-13 in HD patients and its association with AVF thrombosis, and correlate the level of ADAMTS-13 with age, duration of dialysis, certain hematological parameters and estimated GFR.

Patients and Methods

This study applied on 60 patients with ESRD on well orderd HD sessions from two dialysis health centers; in Baghdad Teaching Hospital of Medical City and AL -Karama Teaching hospital, spaning a period from 21 January 2020 to 21 June 2020. A total of 60 subjects were participate in this study, all of them use AVF as an access for hemodialysis, 30 patients of them with a previous history of fistula thrombosis and the remaining 30 patients was without such history, and 20 age and gender-matched healthy subjects as controls. 2ml of venous blood were collected from each person in the groups with a septic precautions, then was centrifuged for 15 min at 1000 rpm, Plasma was stored at (−80∘C) at National Center of Teaching Laboratories in Medical city until plasma ADAMTS-13 ELISA assay was done using ADAMTS13 kit, Quantikine, USA [14]. Patients with a history of malignant disorders, liver diseases (including hepatitis), vasculitis, pregnancy, history of renal transplantation, TTP, history of recent traffic accidents in less than 6 months and a family history of hereditary thrombophilia, patients with a history of primary AVF failure which was thrombosed in the period prior dialysis beginning , was excluded.

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Statistical Analysis

The data analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented by frequencies . Both independent t-test and Analysis of Variance (ANOVA) ; (two tailed) was used to compare the indices. Pearson's correlation test (r) was used to assess correlation between continuous variables accordingly. Receiver operating characteristic (ROC) curve used for analysis of plasma ADAMTS 13 level for prediction of AVF thrombosis.

Results

The mean age of participant in this study was 53.5. Regarding gender, patients with AVF thrombosis were distributed equally while patients without AVF thrombosis was 60% males versus 40% in females. The duration of dialysis was ≤ three years in 70% and 66.7% of patients with AVF thrombosis and those without AVF thrombosis , respectively. The comparison between study groups in mean of eGFR as in the Table (1) which clarify that it was more in controls than that in both patients with and without fistula thrombosis, and was significantly higher in patients without AVF thrombosis than those with fistula thrombosis .

Table (1): The comparison between study groups in mean of eGFR

	HD patients with AVF thrombosis Mean ± SD, Range	HD patients without AVF thrombosis Mean ± SD, Range	Control Group Mean ± SD. Range	P - Value
eGFR	6.63 ± 2.85(3-15)	9.16 ± 2.54(5.5-22)	94.05 ± 3.3(90-95)	0.001
	6.63 ± 2.85(3-15)	9.16 ± 2.54(5.5-22)	-	0.001

Regarding the haematological indices, the participants in control group were with the highest means of HCT%, Hb, and platelets. In patients groups with AVF thrombosis, the WBC and MPV was higher in comparison with the other patient group Table (2).

Table (2): Comparism between patient groups regarding the haematological indices

CBC Parameters	HD patients with AVF thrombosis Mean ± SD	HD patients without AVF thrombosis Mean ± SD	Control Mean ± SD	P - Value
HCT%	25.8 ± 4.72	27.1 ± 5.34	38.1 ± 2.35	0.001
Hb g/dl	8.6 ± 1.57	9 ± 1.78	12.7 ± 0.78	0.001
WBC $10^3/\mu L$	8.1 ± 2.85	7.1 ± 2.92	7.6 ± 1.83	0.348
Platelets $10^9/\mu L$	160.2 ± 82.34	141.4 ± 77.41	280 ± 105.1	0.001
MPV (FL)	9 ± 1.69	8.2 ± 1.44	6.6 ± 1.61	0.001

The comparison between both patients groups with and without fistula thrombosis brightened up that no significant differences in any haematological indices as in Table (3).

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Table (3): Comparism between both patients groups with and without fistula thrombosis regarding hematological indices significance

CBC Parameters	HD patients with AVF thrombosis Mean ± SD	HD patients without AVF thrombosis Mean ± SD	P - Value
HCT%	25.8 ± 4.72	27.1 ± 5.34	0.369
Hb g/dl	8.6 ± 1.57	9 ± 1.78	0.363
WBC 10^3/iL	8.16±2.85	7.16±2.92	0.183
Platelets 10^9/iL	160.2 ± 82.34	141.4 ± 77.41	0.365
MPV (FL)	9 ± 1.69	8.2 ± 1.44	0.07

ADAMTS-13 levels; The comparison in terms of ADAMTS-13 levels between the three study groups showed a highly significant decrease in HD groups compared to the control group (137.69 ng /ml in HD patients with AVF thrombosis, 248.76 ng/ml in HD patients without AVF thrombosis versus 413.25 ng/ml in control group, as shown in Table (4) and Figure (1).

Table (4): The comparison in terms of ADAMTS-13 levels

ADAMTS-13 (ng/ml)	HD patients with AVF thrombosis Mean ± SD, Range	HD patients without AVF thrombosis Mean ± SD, Range	Control Group Mean ± SD Range	P - Value
	137.69 ± 60.65	248.76 ± 58.81	413.25 ± 123.26	**0.001**

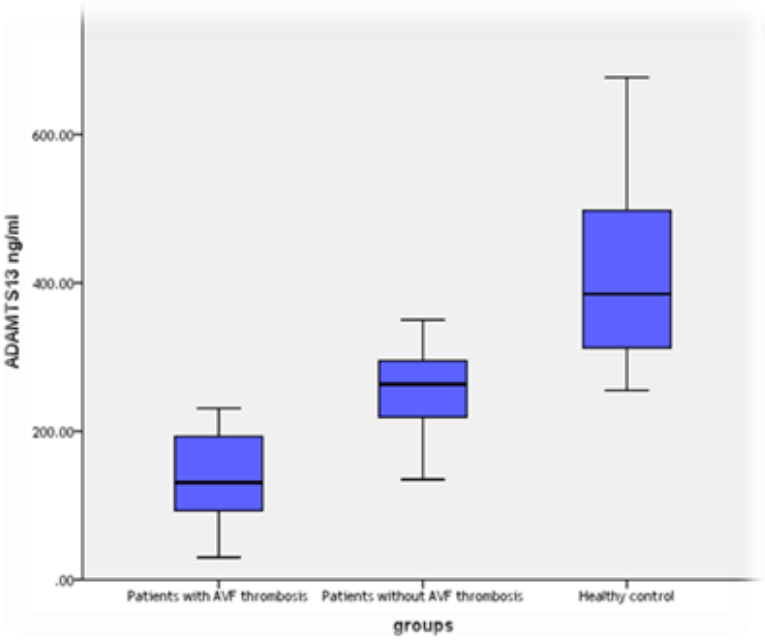

Figure (1): Comparison between study groups in terms of plasma ADAMTS-13

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HD patients with AVF thrombosis had a significantly lower levels of plasma ADAMTS-13 than HD patients without thrombosis (137.69 ng/ml versus 248.76 ng/ml, P= 0.001) as described in Table (5).

Table (5): Significance comparism regarding ADAMTS-13

ADAMTS-13 (ng/ml)	HD patients with AVF thrombosis Mean ± SD, Range	HD patients without AVF thrombosis Mean ± SD	P - Value
	137.69 ± 60.65(55-260)	248.76 ± 58.81(195-410)	**0.001**

Curve of receiver operating characteristic (ROC) was used to determine the point of plasma ADAMTS-13 level according to which prediction of AVF thrombosis occurrence in HD patients is supposed to happen, Figure (2).

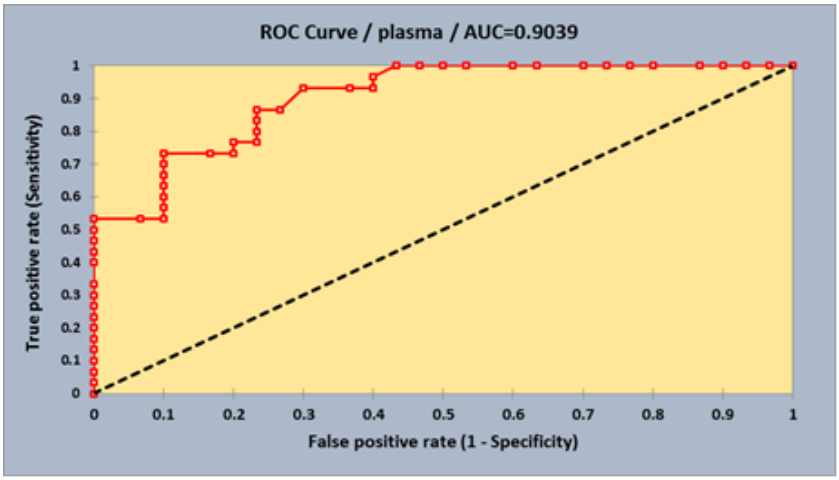

Figure (2) : ROC curve for ADAMTS-13

ADAMTS-13 was 73.3% sensitive, 90% specific, and 81.6% accurate as a marker for prediction of AVF thrombosis among patients undergoing HD. A significant positive correlation was found between ADAMTS-13 level and eGFR (r= 0.728, P= 0.001), as shown in the Figure (3).

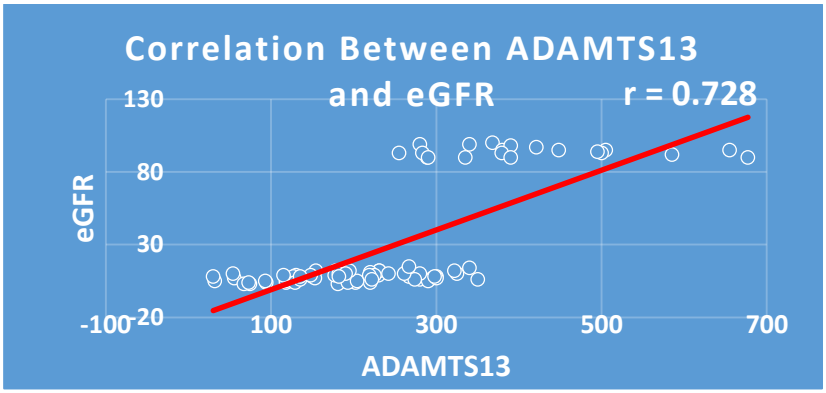

Figure (3) : Correlation between ADAMTS 13 and eGRR

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ADAMTS-13 level was significantly, positively correlated with platelets (r= 0.479) with P- value of 0.001, and inversely correlated with MPV (r= - 0.438, P= 0.001) as shown in Figure (4, 5).

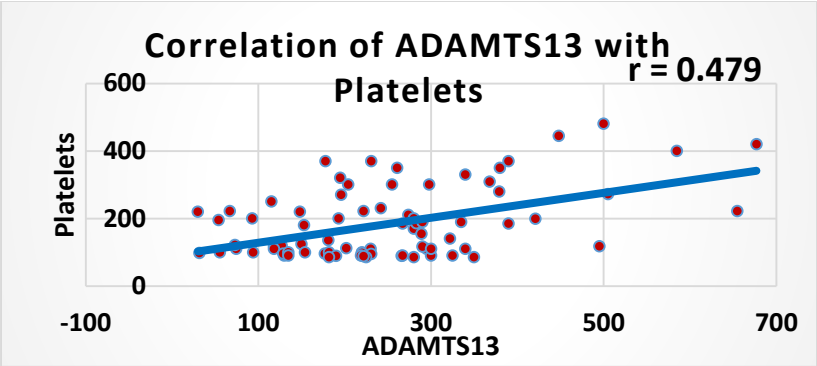

Figure (4): Correlation between ADAMTS 13 and platelet

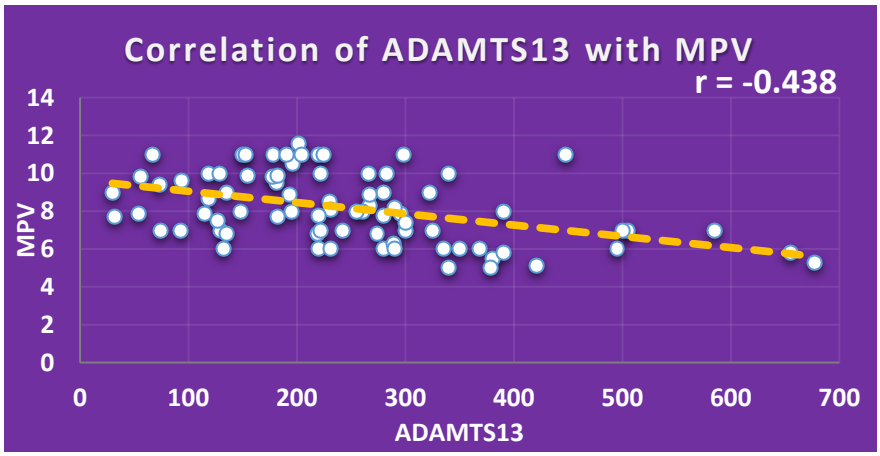

Figure (5): Correlation between ADAMTS13 and MPV

Discussion

The complications that occur to the vascular access contribute to 20–25% of all hospitalizations in dialysis patients , around 85% of these cases are due to thrombosis[15]. In present study, the mean age, of ESRD patients included were comparable with the mean age in other Iraqi studies like Al-Rubaie HA[16], Murtadha NA[17], Khaleel FM [18], also there was no significant difference founded between the mean age of the 3 study groups, this result was comparable to Gaur P *et al* [19], but not in agreement with Gameiro J *et al* [20], regarding the duration of hemodialysis, no statistically significant difference present between both HD groups, this result was similar to Rios DR *et al*. [7]. Elzorkany KM et al. 21 and was not in agreement with Abd El Hady H *et al*.[22]. Hadhri S *et al*.[23] that suggest to consider the duration of hemodialysis as a risk factor contribute to access thrombosis. The insignificant difference in the current result regarding the duration of hemodialysis may be due to differences in the sample sizes and may be due to inclusion criteria that include the patients on maintenance HD and excluding those with recently onset dialysis. The estimated glomerular filtration rate is generally the most useful index for kidney function, which should be estimated using

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estimating CKD-EPI equation. 24 HD patients had significant lower eGFR compared to healthy control group, this result was comparable to Dubin R *et al*. [25]. In addition to that, the eGFR in the HD patients with fistula thrombus were significantly less compared to the those without AVF thrombosis (6.63 versus 9.16) mL/min , with P-value of 0.001. Significant statistical differences was found when comparison done in term of Hb, HCT%, Platelet count, MPV but not in WBC count, and insignificant difference was seen between the two HD patients groups regarding the mentioned haematological parameters. Al-Rubaie HA *et al*.[16] study say that no significant difference between patients and healthy regarding WBC count, but significant differences in other hematological parameters. Elzorkany KM *et al* [21] conclude no significant differences present between the HD patients in regards to Hb level, Abdelhafez M *et al*.[26] conclude that a significant decrease in platelets count of HD patients was found when compared to healthy study group.

Ahmed *et al*. [27] concluded that there was a significant difference of platelets count and MPV between study groups as the platelets count was significant decreased and MPV was significant increased in the HD patients. Gheissari A *et al*. [28] conclude that a statistical significant difference in ESRD patients and control as the former has lower platelets value and higher MPV than the latter. Comparison regarding the mean ADAMTS-13 level show a highly significant decrease of mean plasma ADAMTS-13 in HD groups compared with the control group and a significantly lower in dialyzed patients with AVF thrombus than HD patients without AVF thrombosis. Our result was in aggrement with Rios DR *et a*l [15]. Which conclude that decreased ADAMTS-13 levels in patients compared to the healthy , and they suggest that this may be due to the hypercoagulable condision occur in those patients and they found that there was no significant difference between HD patients with and without AVF thrombosis for mean of ADAMTS13 levels. The result that founded by our study is in align with Abd El Hady H *et al*.[22]. Who conclude that mean ADAMTS-13 level lower in HD patients compared with healthy group, with a highly significant less in ADAMTS-13 levels in HD patients with AVF thrombosis compared with those without thrombosis. Elzorkany KM *et al*.[21] stated that plasma ADAMTS13 might be considered as a marker of hypercoagulability in haemodialysis patients. Abdelhafez M et al 26 was similar to our study but the study done on pediatric age. According to our result, we suggest that decreased ADAMTS-13 Ag level may be a risk factor for AVF thrombosis occurrence and there was a significant positive correlations founded between ADAMST13 level and eGFR, platelet count, and a negative correlation with MPV. This is in aggrement with Taniguchi S *et al*.[29]. Abd El Hady H *et al*.[22]. No correlation was found between ADAMTS-13 levels and duration of dialysis, age, WBC count, Hb, HCT. This is similar to Abdelhafez M et al.[26].

Conclusions

Our result conclude that a significant differences were found between HD patients and control groups regarding eGFR, studied

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hematological parameters and the ADAM-13 level which was significantly less in adult patients with ESRD on maintenance HD compared to healthy persons, Plasma ADAMTS-13 level was significantly less in patients with fistula thrombosus than those without AVF thrombosis. According to our result, decreased ADAMTS-13 Ag level may be a risk factor for AVF thrombosis occurrence so it may be considered as a useful marker for prediction of AVF thrombosis occurrence warning for AVF surveillance.

Recommendations

1-Since ADAMTS13 is an important component of the hemostatic system, the role of this enzyme in the onset of thrombosis in HD patients should be evaluated and further studies with follow up to the patients to prove the association with AVF thrombosis are advised.

2-Measurement of VWF level in synchronous with ADAMTS-13 level is recommended as the imbalance between ADAMTS13 and its substrate (VWF) levels may further support our result and explain the development of thrombosis in AVF.

3-Additional studies to identify other risk factors to AVF thrombosis are warranted and essential for better management of HD patients.

4-Assessment of ADAMTS13 level in both pre and post kidney transplantation, also study its expression on renal tissue are advised and these results may support our study.

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Ethical clearance: The study was approved by the academic ethical committee, Baghdad University.

Conflict of interest: Nil

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مستوى البلازما لـ ADAMTS-13 في مرضى غسيل الكلى المداومة: علاقته بتجلط الناسور الشرياني الوريدي

سجى حمادي فهد [1], ناجحة احمد امين [2]

الملخص

خلفية الدراسة: يُعرَّف مرض الداء الكلوي في مراحله الأخيرة بأنه فقدان وظائف الكلى بحيث تصبح الحياة غير مستدامة في غياب العلاج الكلوي البديل ، والذي يتم توفيره في شكل كلية مزروعة أو بشكل أكثر شيوعًا، غسيل الكلى على المدى الطويل . الناسور الشرياني الوريدي (AVF) هو منفذ الأوعية الدموية المفضل للمرضى الذين يحتاجون إلى غسيل الكلى، والذي تم إنشاؤه عن طريق ربط الشريان بالوريد مما يؤدي إلى تحويل الشرايين إلى الوريد ، مما يسهل استخدامه لاحقًا للوصول إلى الدورة الدموية.

اهداف الدراسة: لتقييم مستوى البلازما لـ ADAMTS-13 في مرضى الغسيل الكلوي وارتباطه بتجلط الناسور الشرياني الوريدي و لربط مستوى ADAMTS-13 مع معدل التصفية الكبيبي الكلوي المقدر ومدة غسيل الكلى ومعلمات الدم.

المرضى والطرائق: تم إجراء دراسة الحالة والشواهد على ستون مريضا بالغًا تم تشخيص إصابتهم بالداء الكلوي بمراحله الأخيرة ويخضعون لجلسات الغسيل الكلوي بصورة منتظمة، وتم اختيارهم بالتتابع وفقًا لمعايير التضمين والاستبعاد ، وتم تضمين عشرين فردًا سليمًا (متطابقين مع العمر والجنس) كمجموعة تحكم. تم اختبار عينات البلازما لمستوى ADAMTS-13 بواسطة تقنية مقايسة الممتز المناعي المرتبط بالإنزيم.

النتائج: كان متوسط مستوى ADAMTS-13 في البلازما أقل بشكل ملحوظ في مرضى الغسيل الكلوي مقارنة بمجموعة المقارنة ($P < 0.001$) ، وكان لدى مرضى الغسيل الكلوي الذين يعانون من تجلط الناسور الشرياني الوريدي متوسط أقل بكثير من مستوى ADAMTS13 في الدم مقارنة بمرضى الغسيل الكلوي الذين لا يعانون من تجلط الناسور الشرياني الوريدي .

الاستنتاجات: مستوى البلازما ADAMTS-13 أقل بشكل ملحوظ في المرضى البالغين الذين يعانون من الداء الكلوي بمراحله الأخيرة يخضعون لعلاج الغسيل الكلوي مقارنة بمجموعة الاشخاص الاصحاء. ب- ADAMTS-13 محدد بنسبة 90٪ وحساس 73.3٪ لذا يمكن اعتباره علامة مفيدة للتنبؤ بالتحذير من حدوث تجلط الناسور الشرياني الوريدي. ت- تم العثور على ارتباط إيجابي قوي بين مستوى ADAMTS-13 و معدل التصفية الكبيبي الكلوي و بعض معلمات الدم(الصفيحات الدموية و معدل حجم الصفيحات الدموية) . لم يتم العثور على ارتباط بين مستوى ADAMTS-13 ومدة غسيل الكلى وعدد كريات الدم البيضاء و الهيموغلوبين و, الهيماتوكريت.

الكلمات المفتاحية: ADAMTS-13، الناسور الشرياني الوريدي، غسيل الكلى، التخثر

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