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Association of Von Willebrand Factor Level and Activity with GIT Bleeding in Adult Hemodialysis-Dependent ESRD Patients

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ABSTRACT

Background: Patients with end-stage kidney disease (ESKD) undergoing hemodialysis, peritoneal dialysis, or kidney transplantation are prone to bleeding complications, partly due to alterations in von Willebrand factor (vWF), a key protein in blood coagulation. Dysfunction or abnormal concentration of vWF may contribute to gastrointestinal (GIT) bleeding.

Aim: This study aimed to evaluate the relationship between vWF levels/activity and GIT bleeding in adult hemodialysis-dependent ESKD patients.

Patients and methods: A case-control study was conducted at Menoufia University Hospital and Mit Ghamr Nephrology and Urology Hospital over four years (Jan 2021–Dec 2024), including 53 end-stage renal disease (ESRD) patients on maintenance hemodialysis and 48 healthy controls.

Results: Among ESRD patients, 7.5% had clinically evident GIT bleeding (three upper & one lower), and 11.3% had positive occult blood tests (two false positives). vWF antigen (vWF-Ag) levels correlated positively with INR (r=0.349, p=0.01) and serum creatinine, and negatively with GFR. vWF ristocetin cofactor activity (vWF:RCo) also correlated positively with INR. Univariate analysis linked lower albumin, higher vWF-Ag, and higher vWF:RCo to increased GIT bleeding risk. In multivariate analysis, vWF:RCo was an independent predictor. Diagnostic performance showed vWF-Ag had 100% sensitivity, 79.3% specificity, PPV of 40% and AUC of 0.948. vWF:RCo had 100% sensitivity, 77.3% specificity, PPV of 28.6% and AUC of 0.841.

Conclusion: vWF dysfunction contributed to GIT bleeding risk in hemodialysis-treated ESRD patients. Both vWF-Ag and vWF:RCo were associated with bleeding, but vWF:RCo independently predicts risk, suggesting its potential as a biomarker for identifying high-risk patients.

Keywords: ESRD, von Willebrand factor, Gastrointestinal bleeding.

INTRODUCTION

A worldwide public health concern is end-stage renal illness that necessitates frequent renal replacement treatments, such as hemodialysis, transplantation, and peritoneal dialysis [1]. According to the 2024 International Society of Nephrology (ISN)-Global Kidney Health Atlas, the median worldwide incidence of treated end-stage renal disease (ESRD) needing kidney replacement treatment (KRT) was 146 cases per million population (pmp) [2]. Chronic renal disease patients are more likely than the general population to experience intestinal bleeding, which also has a higher fatality rate.

The hemostatic problems linked to chronic renal illness have been blamed for the increased risk and severity of hemorrhage in these instances [3]. One of the most important components of the hemostatic system is von Willebrand factor (vWF). Because it promotes platelet adhesion, platelet plug formation, and factor VIII stability, this glycoprotein is crucial for hemostasis [4].

It is proposed that angiogenesis, endothelial cell proliferation, and angiodysplasia can be caused by defective or inadequate von Willebrand factor.

Gastrointestinal bleeding can be caused by changes in the gastrointestinal system [5]. Laboratory results and clinical manifestations of acquired von Willebrand syndrome (AvWS), an uncommon but likely underdiagnosed bleeding illness, are comparable to those of inherited vWD [6]. Differentiating from vWD, a bleeding condition caused by quantitative or qualitative genetic abnormalities of vWF [7]. Patients with AvWS may also experience gastrointestinal hemorrhage.

In order to rule out ulcers, polyps, or cancer as potential causes of GI bleeding, an endoscopic examination of the GI tract is required. Prophylactic vWF/factor VIII concentrates are typically initiated following GI bleeding events in congenital vWD [8]. It is commonly known that patients with ESRD and chronic kidney disease (CKD) have significantly higher levels of vWF antigen [9]. The majority of research on the coagulation process in CKD is restricted to patients receiving hemodialysis who have ESRD [10].

In hemodialysis-dependent ESRD patients, the potential correlations between von Willebrand factor deficiency level and activity and GIT hemorrhage remain unclear. In adult patients with hemodialysis-dependent

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end-stage renal illness, the purpose of this study was to evaluate the relationship between von Willebrand factor (both level and activity) and GIT hemorrhage.

PATIENTS AND METHODS

This case-control research has been performed in the Hemodialysis Units of Menoufia University Hospital and Mit Ghamr Nephrology and Urology Hospital. The study included 101 subjects, comprising 53 ESRD cases on maintenance hemodialysis and 48 apparent healthy volunteers. The study spanned a duration of four years, from January 2021 to December 2024.

Inclusion criteria: Adults > 18 years old and ESRD ≥ 6 months on hemodialysis.

Exclusion criteria: Patients with gastrointestinal (GIT) malignancies, a history of inflammatory bowel disease (IBD), chronic liver disease or abnormal liver tests, hereditary blood diseases, or those who received oral anticoagulants within the last month or oral iron supplements within the last six months. Additionally, patients with ongoing active infections (less than two weeks) or those taking medications that could affect von Willebrand factor levels.

All cases have been exposed to complete history taking, physical examinations, and routine laboratory examinations that involved CBC, blood urea and creatinine levels, measurements of calcium (total and ionized), phosphorus, and parathyroid hormone (PTH), as well as liver tests (ALT, AST, and albumin). Coagulation profiles such as PT, PTT, and INR were also assessed. Additionally, tests for occult blood in stool and evaluations of vWF level and activity were conducted.

Sandwich ELISA was used to test the levels of von Willebrand factor antigen (vWF-Ag) (Human vWF-Ag ELISA Kit, Sunredbio, China; Cat. No. 201-12-1141). Monoclonal anti-vWF antibodies, biotinylated detection antibodies, and an HRP-Streptavidin complex were incubated with plasma samples. Optical density (OD) was measured at 450 nm following substrate addition, and concentrations were computed using a standard curve. The test had a sensitivity of 0.663 ng/mL and a detection range of 0.75–200 ng/mL **[11].**

Von Willebrand factor activity (vWF:RCo) assay values were assessed using a platelet-binding ELISA (Human vWF ELISA Kit, DL Develop, China; Cat. No. DL-vWF-Hu). The assay quantified vWF's functional interaction with ristocetin, with OD readings at 450 nm. The detection range was 50– 200 IU/dl with a sensitivity of 0.53 ng/mL **[12].**

Patients were also classified based on the cause of ESRD, such as hypertension or diabetes, and the prevalence of GIT bleeding was compared across these groups using appropriate statistical methods.

Ethical Approval: Before the study began, all participants provided written informed consents. The study was approved by The Local Ethical Research Committee of Menoufia Faculty of Medicine. Furthermore, the study received formal approval from The Institutional Review Board. The research was carried out following established ethical guidelines, of The Declaration of Helsinki and its subsequent updates [under code no. 1/2021-INTM4].

Statistical analysis

The gathered data have been encoded, processed, and analyzed utilizing the SPSS software (Version 25) for Windows. Descriptive statistics have been computed to encompass standard deviations, means, ranges, medians, and percentages. Independent t-tests have been conducted to compare the means of regularly distributed continuous variables, while Mann–Whitney U test was utilized to assess median variations in non-normally distributed data, and Chi-square test was utilized for categorical data. The t-test and Wilcoxon test was utilized for dependent groups. Chi-square and t-tests were utilized to compare the duration of hemodialysis between patients with and without GIT bleeding. Additionally, vWF levels and activity have been analyzed by comparing patients with positive versus negative occult blood in stool using t-test or Mann-Whitney U test. Similarly, vWF levels and activity were compared between patients with clinically evident GIT bleeding and those without bleeding, employing the same statistical approaches. A p-value ≤ 0.05 was deemed statistically significant.

RESULTS

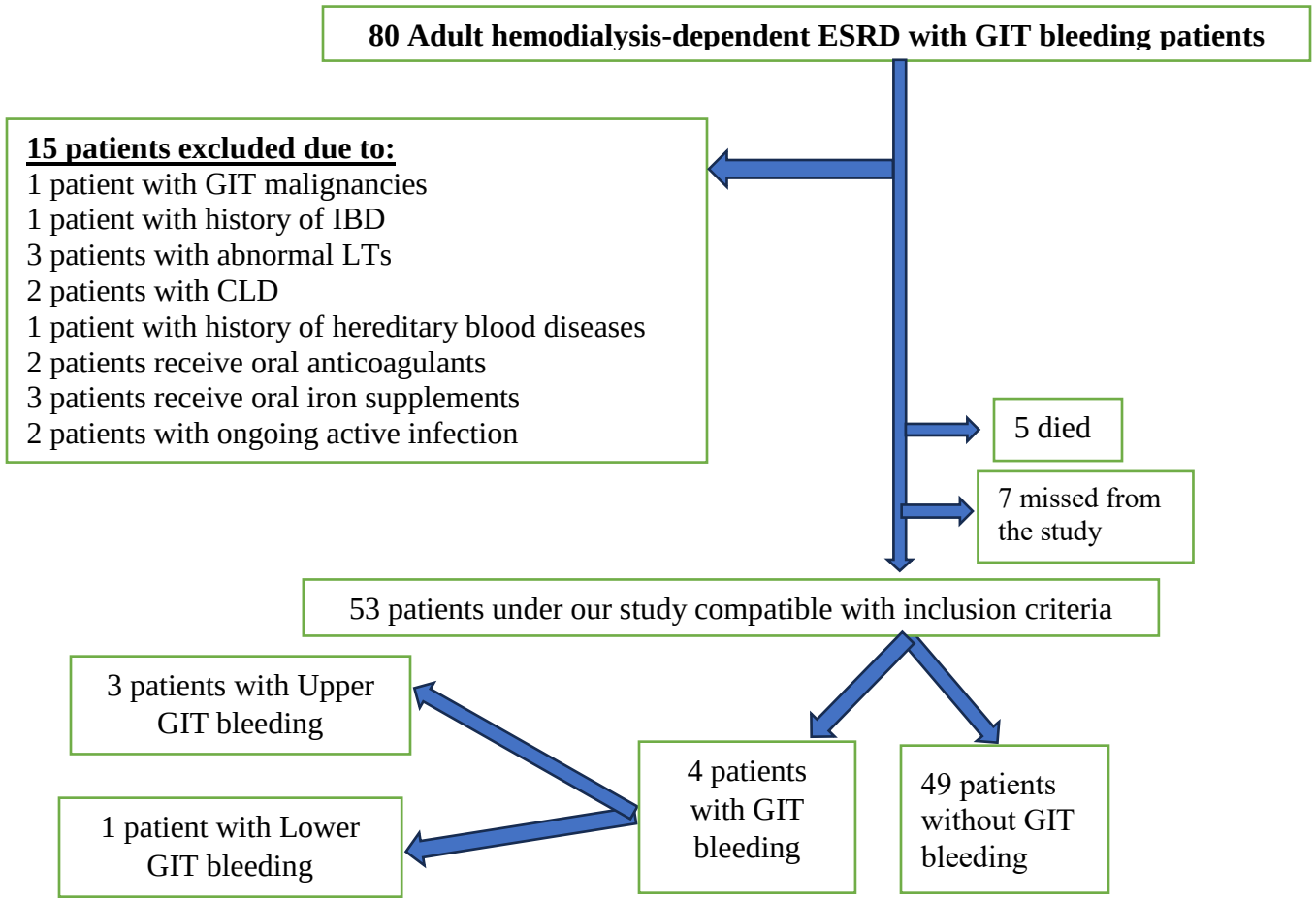

Figure (1): Flowchart of the patients.
IBD: inflammatory bowel diseases, ESRD: end-stage renal disease, GIT: gastrointestinal tract, LTs: liver tests, CLD: chronic liver diseases.

The mean age in the study group (HD cases) was 53.09 ± 16.06 years, with 58.5% of cases being females with a mean weight of 74.68 ± 15.31 kg. In the control group, the mean age was 48.65 ± 8.56 years, and 56.3% of cases were females with a mean weight of 78.15± 19.24 kg. Insignificant variations were detected among both groups according to gender, weight, and age (p-value above 0.05) (Table 1).

Table (1): Comparison between both groups as regards gender, age & weight.

		HD patients (N=53)		Controls (N=48)		Test value	P-value
		No.	%	No.	%		
Gender	**Male**	22	41.5%	21	43.8%	X^2= 0.052	0.820
	Female	31	58.5%	27	56.3%		
Age (year)	**Mean± SD**	53.09± 16.06		48.65± 8.56		T = 1.711	0.082
	Range	24 – 85		34 - 73			
Weight (Kg)	**Mean± SD**	74.68± 15.31		78.15± 19.24		T = 1.005	0.317
	Range	49 – 125		54 – 139			

The control group had a vWF-Ag level of 12.7 (11.0–60), whereas HD patients had a median (range) level of 16.03 (7.28–240). HD patients' median (range) of vWF:RCo levels were 111.95 (8.27–493.33), but the control group's was 70.48 (40.9–320.72). Compared to the control group, HD cases had significantly higher levels of both vWF:RCo and vWF-Ag values ($p < 0.001$ & $p < 0.001$, respectively). HD patients had higher vWF activity than controls (35.8% vs. 2.1%), as seen in table (2).

Table (2): Comparison between ESRD patients on hemodialysis and controls regarding vWF-Ag level , vWF:RCo values & vWF-activity (%).

		HD patients		Controls		Test value	P-value
		N	%	N	%		
vWF-Ag (ng/ml)	**Mean± SD**	31.35± 4.02		17.94± 1.72		$^{Z}_{MWU}$= 2.627	**<0.001****
vWF:RCo values (IU/dl)	**Mean± SD**	208.86± 15.61		80.15± 4.85		$^{Z}_{MWU}$= 5.224	**<0.001****
vWF-activity (%)	**Low**	1	1.9%	3	6.3%	X^2= 18.569	**<0.001****
	Normal	33	62.3%	44	91.7%		
	High	19	35.8%	1	2.1%		

Out of 53 patients, four patients (7.5%) reported GIT bleeding; three of them had upper GIT bleeding, while one case had lower GIT bleeding. Positive occult blood was noticed in six (11.3%) cases, as two cases had false positive results as shown in table (3).

Table (3): GIT bleeding and occult blood among the studied patients

		Studied patients (N= 53)	
		N	%
GIT bleeding	**No**	49	92.45%
	Yes	4	7.55%
	• Upper GIT bleeding	3	5.66%
	• Lower GIT bleeding	1	1.89%
Occult blood	**Negative**	47	88.7%
	Positive	6	11.3%

Upper GI endoscopy revealed peptic ulcer in one case, the second case showed drug-induced esophagitis, the third case showed angioectasia, while the last fourth case by lower endoscopy revealed angiodysplasia. While, vWF-Ag level and GFR had a significant negative correlation (r-value = -0.297, p-value = 0.003), there was a substantial positive correlation with INR (r = 0.396, p = 0.003) and serum creatinine (r = 0.324, p = 0.001). vWF:RCo values and INR showed a substantial positive correlation (r-value = 0.349, p-value = 0.01), as seen in (Table 4).

Table (4): Correlation between vWF-Ag levels and vWF:RCo values with various numerical parameters

	vWF-Ag levels	**vWF-Ag** levels	**vWF:RCo values**	**vWF:RCo values**
	SPr	**P-value**	**SPr**	**P-value**
Age (years)	-0.127	0.364	-0.023	0.870
Weight (Kg)	0.192	0.168	0.033	0.815
ALT (U/L)	0.179	0.199	0.176	0.207
AST (U/L)	0.129	0.359	0.086	0.539
S. creatinine (mg/dl)	**0.324**	**0.001****	0.043	0.758
GFR (mL/min/1.73 m²)	**-0.297**	**0.003****	-0.042	0.763
Hemoglobin (g/dl)	0.01	0.944	-0.019	0.892
TSAT %	0.117	0.405	0.209	0.132
Ferritin (ng/ml)	-0.081	0.566	0.093	0.508
PTH (pg/ml)	-0.15	0.282	0.02	0.888
Total calcium (mg/dl)	0.01	0.945	0.022	0.876
Ionized calcium (mmol/L)	0.194	0.163	0.175	0.209
Phosphorus (mg/dl)	0.129	0.359	-0.263	0.057
PT (sec.)	0.055	0.694	-0.036	0.796
PTT (sec.)	0.177	0.204	-0.015	0.913
INR	**0.396**	**0.003****	**0.349**	**0.010****
Albumin (g/dl)	0.111	0.430	-0.081	0.564
Hemodialysis duration (year)	0.028	0.842	0.004	0.978

The level of vWF:RCo values were significantly higher in CKD patients with GIT bleeding than in CKD patients without GIT bleeding (p=0.025), while a non-significant difference was detected among CKD cases with and without bleeding regarding vWF-Ag level and duration of hemodialysis (p >0.05) (table 5).

Table (5): Comparison of vWF-Ag level and activity among cases with and without GIT bleeding in ESRD patients on hemodialysis.

		CKD without GIT bleeding (N= 49)	CKD with GIT bleeding (N= 4)	Test value	P-value
vWF-Ag (ng/ml)	**Mean± SD**	26.21± 4.82	94.38± 10.35	$^{Z}_{MWU}$= 0.017	0.987
vWF:RCo values (IU/dl)	**Mean± SD**	142.36± 36.29	276.79± 60.52	$^{Z}_{MWU}$= 2.247	**0.025***

In univariate analysis, lower albumin levels, higher vWF-Ag levels, and higher vWF:Co-values were positively correlated with enhanced risk of GIT hemorrhage as shown in table (6).

Table (6): Univariate Logistic regression analysis for factors predicting GIT bleeding in ESRD patients on hemodialysis.

Parameters	Univariate			
	P-value	Odds ratio (OR)	95%CI	
			Lower limit	Upper limit
Age (year)	0.070	1.074	0.994	1.16
Gender (male)	0.760	0.732	0.099	5.415
Weight (Kg)	0.417	1.021	0.971	1.072
ALT (U/L)	0.487	0.935	0.773	1.131
AST (U/L)	0.587	1.05	0.881	1.252
S. creatinine (mg/dl)	0.161	1.579	0.833	2.993
GFR (mL/min/1.73 m^2)	0.134	0.571	0.274	1.188
Hemoglobin (g/dl)	0.200	1.447	0.822	2.546
TSAT %	0.747	1.031	0.855	1.244
Ferritin (ng/ml)	0.690	0.996	0.978	1.015
PTH(pg/ml)	0.616	1.006	0.982	1.032
Total calcium (mg/dl)	0.220	2.327	0.603	8.984
Ionized calcium (mmol/L)	0.564	3.676	0.044	305.147
Phosphorus (mg/dl)	0.706	1.154	0.548	2.431
PT (sec.)	0.245	2.085	0.604	7.193
PTT (sec.)	0.646	0.939	0.719	1.227
INR	0.183	17.396	0.26	1162.308
Albumin (g/dl)	**0.012***	0.151	0.034	0.662
vWF-Ag level (ng/ml)	**0.012***	1.028	1.006	1.05
vWF:RCo-values (IU/dl)	**0.016***	1.008	1.001	1.014

Table (7) explained the link between vWF:RCo-values and GIT bleeding in hemodialysis patients with ESRD and multivariate analysis using a model adjusted for the previously described parameters.

Table (7): Multivariate Logistic regression analysis for factors predicting GIT bleeding in ESRD patients on hemodialysis.

Parameters	Multivariate			
	P-value	Odds ratio (OR)	95%CI	
			Lower limit	Upper limit
Albumin (g/dl)	0.097	1.007	0.999	1.016
vWF-Ag level (ng/ml)	0.133	1.029	0.991	1.068
vWF:RCo-values (IU/dl)	**0.037***	0.065	0.005	0.845

The value of vWFAg levels and vWFR:Co values in predicting GIT bleeding in ESRD patients receiving hemodialysis was ascertained using receiver operating characteristic (ROC) analysis. For **vWF-Ag** (at cut-off of 23.3 ng/ml), the test exhibited 100% sensitivity and 100% NPV, making it highly effective in ruling out GIT bleeding in ESRD patients on hemodialysis. Its specificity was 79.3% with a PPV of 40%. A high AUC of 0.948 demonstrated excellent diagnostic accuracy, and it was statistically significant ($p < 0.001$). For **vWF:RCo** (at cut-off of 172 IU/dl), the test showed 100% sensitivity and 100% NPV, reinforcing its effectiveness in excluding GIT bleeding risk. However, its specificity was slightly lower 77.3%, and PPV was 28.6%, suggesting a higher rate of false positives compared to vWF-Ag. When its AUC was 0.841, it remained statistically significant ($p< 0.001$), indicating a meaningful association with GIT bleeding in ESRD patients as shown in table (8).

Table (8): Validity (AUC, sensitivity, specificity) for vWF Ag levels and vWF:RCo values in prediction of GIT bleeding in ESRD patients on hemodialysis.

	Best cut off	Sensitivity	Specificity	PPV	NPV	AUC	P-value
vWFAg levels	23.3	100%	79.3%	40%	100%	0.948	**<0.001****
vWF:RCo values	172	100%	77.3%	28.6%	100%	0.841	**<0.001****

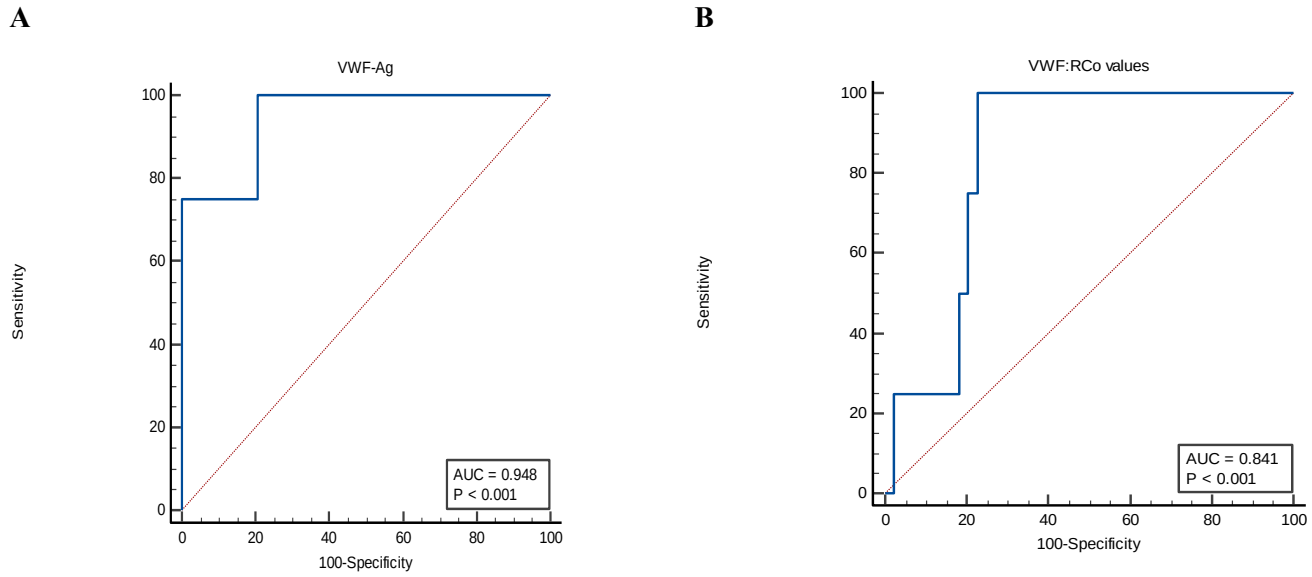

Figure (1): (A): ROC curve of vWF-Ag level in prediction of GIT hemorrhage in ESRD cases on hemodialysis. **(B)**: ROC curve of vWF:RCo-values in prediction of GIT hemorrhage in ESRD cases on hemodialysis.

DISCUSSION

A glomerular filtration rate of less than sixty milliliters per minute (1.73 millimeters) and a duration of more than three months are indicative of irreversible renal damage or reduced renal function, which is known as chronic kidney disease (CKD) [13, 14].

In order to evaluate their levels in GI bleeding, we looked at both vWF-Ag and vWF:RCo values in patients with hemodialysis-dependent ESRD. We discovered that HD cases had considerably higher levels of vWF-Ag and vWF:RCo than the control group, and that HD cases had higher levels of vWF activity than controls (35.8% versus 2.1%). Moreover, we found that the vWF:RCo values was significantly higher in CKD patients with GIT bleeding compared to CKD patients without GIT bleeding. In GIT bleeding in ESRD patients, vWF-Ag at best cut off level showed 100% sensitivity and 79.3% specificity, with a PPV of 40% and an AUC of 0.948.

Also, vWF:RCo best cut off value showed 100% sensitivity and 77.3% specificity, with a PPV of 28.6%, and an AUC of 0.841, indicating its potential as a predictor for GIT bleeding in these patient population. These are similar to those of **Rios *et al.*** [15] who sought to investigate how ABO blood types affected the plasma concentrations of ADAMTS13, FVIII activity, and vWF in hemodialysis patients. The cross-sectional study included 80 healthy volunteers and 195 hemodialysis patients who were sourced from two dialysis facilities in Brazil. Age and gender differences between the two groups were statistically insignificant (P-value was over the 0.05 threshold). Our results are consistent with those of **Yousuf *et al.*** [16] who sought to assess vWF plasma concentrations in patients receiving continuous hemodialysis in order to ascertain how much of a role it plays in the prevalence of vascular access thrombosis (VAT) in this demographic. With high statistical significance, the HD groups' mean vWF serum level was significantly higher (GI 1361.47 ± 270.38 and GII 950 ± 138.12) than that of the control group (351.5 ± 34.8). Additionally, **Yen *et al.*** [17] showed that the HD and CKD groups had considerably higher levels of vWF antigen and activity than in the control group.

In our study, we found that there was a significant positive association among vWF-Ag level and INR and serum creatinine (r-value = 0.324, p-value = 0.001). The reason of INR rise although exclusion of patients who received oral anticoagulants through last month may be due to the ordinary use of UFH and LMWH as anticoagulants to prevent thrombosis during hemodialysis session. However, it might be a false elevation, as demonstrated by **Leech *et al.*** [18] who found that an INR value that is erroneously inflated because of reagent sensitivity that might lead to an early termination of heparin therapy and put some patients at short-term risk for recurrent thrombosis.

Our research revealed a strong inverse relationship between GFR and vWF-Ag level. Gender and the cause of CKD did not significantly correlate with vWF-Ag level ($p > 0.05$). This outcome is similar to that of **Shen *et al.*** [19] who found a significant negative connection between GFR and vWFAg levels ($r = -0.194$, $P = 0.04848$). The following are some potential explanations for this association, whereas chronic kidney disease (CKD) worsens, many renal units sustain damage, which impairs normal excretory function and decreases the elimination of procoagulant chemicals. Furthermore, a great deal of research has shown that vWF, fibrinogen, and FVIII are linked to the inflammatory response. Procoagulant factors can be activated by proinflammatory substances as cytokines, which raises certain hemostatic factor levels [20].

Two of the six occult bleeding instances in our study were false positives, and the four gastrointestinal bleeding cases were split into three upper gastrointestinal bleeding cases and one lower gastrointestinal bleeding case. One patient had a peptic ulcer discovered by upper endoscopy, another had drug-induced esophagitis, a third had angioectasia, and a lower endoscope indicated angiodysplasia. Our results are consistent with **Oakland's** [21] findings, which indicate that CKD patients who experience upper gastrointestinal bleeding due to peptic ulcers fare worse than the overall population. The Rockall score and other mortality prediction systems include renal insufficiency. Similarly, Mallory-Weiss rips, tumors, esophagitis, and Dieulafoy's lesions were among the other bleeding sources that **Antunes *et al.*** [22] and **Chaudhary *et al.*** [23] found in CKD patients. Patients with chronic kidney disease are more likely to experience bleeding from esophagitis, which can be brought on by reflux, infections, medications, or eosinophilic inflammation. Treatment focuses on the root cause and may include mechanical hemostasis and endoscopic procedures. Our findings are consistent with **Costa-Moreira *et al.*** [24], who noted a higher incidence of angioectasias in ESRD patients, possibly due to more frequent bleeding from uremic platelet dysfunction.

Similarly, **Tsai *et al.*** [25] reported that angiodysplasia accounts for 19–32% of lower GI bleeding in dialysis patients, compared to 5–6% in the general population. Additionally, our results align with **Ramdeen** [26], who highlighted angiogenesis as a vascular abnormality with unclear etiology, linked to aging, CKD, aortic stenosis, von Willebrand disease, and LVADs, and often presenting as anemia or GI bleeding.

Another fundamental result in our study that vWF:RCo values was significantly higher in CKD patients with GIT bleeding compared to CKD patients without GIT bleeding ($p = 0.025$), while non-significant variance has been detected among CKD cases with and without bleeding regarding vWF-Ag level ($p > 0.05$). In

contrast to our research, **Gerson *et al.*** [27] found that a number of factors could be responsible for the increase in gastrointestinal bleeding. Because of the uremic state, chronic kidney disease patients primarily show intrinsic platelet dysfunction. Reduced von Willebrand factor activity results from anomalies in platelet function and platelet-vessel wall metabolism, which are correlated with uremia.

Lower albumin levels, higher vWF-Ag levels, and higher vWF:RCo values were all positively correlated with an increased risk of GIT bleeding, according to the current study. Multivariate research using a model adjusted for the above mentioned parameters showed that in hemodialysis patients with end-stage renal illness, the vWF:RCo value was an independent predictor of GIT bleeding. Our findings are in line with those of **Liang *et al.*** [28] who discovered that a history of upper gastrointestinal bleeding (P-value <0.001) and lower serum albumin levels (P=0.004) were independently linked to an elevated risk of upper gastrointestinal hemorrhage.

We assessed the predictive significance of vWF:RCo values and vWF-Ag levels for gastrointestinal bleeding in hemodialysis patients with end-stage renal disease. The vWF-Ag level showed 100% sensitivity and 79.3% specificity, with a 40% PPV and a 100% NPV at a threshold of 23.3. Additionally, it was statistically significant ($p<0.001$) and had an AUC of 0.948. Furthermore, with 100% sensitivity and 77.3% specificity, a PPV of 28.6%, and a 100% NPV at a threshold of 172, the vWF:RCo values were statistically significant ($p<0.001$) at AUC of 0.841.

According to **Yousuf *et al.*** [16] the optimal cutoff point for vWF to detect VAT in dialysis patients is 1277 ng/ml, with 96.67% accuracy, 93.33% sensitivity, 100% specificity, 100% PPV, and 93.8% NPV. Our findings are in line with their findings. Contrary to our study and that of **Leimkühler *et al.*** [29], a vWD is believed to be an unappreciated cause of unexplained bleeding. When vWF adheres to tumor cells or hydroxyethyl starch, is removed by autoantibodies, or is physically changed by shear stress and simultaneously broken by enzymes, it can lead to an acquired deficiency of vWF and a bleeding disorder**.**

The findings of **Elzorkany *et al***. [30] however, they examined the levels of plasma vWF and the proteolytic enzyme ADAMTS13 (a disintegrin and metalloproteinase with eight thrombospondin type 1 motif, 13) in hemodialysis patients and their correlation with vascular access thrombosis, are in line with our findings. Large vWF molecules are broken down by ADAMTS13, which is mostly produced by the liver, avoiding their accumulation on blood vessel walls. Given that vWF is the sole known target of ADAMTS13, an excess of vWF can result from an ADAMTS13 deficiency or antibodies, which may exacerbate thrombosis in dialysis patients. Dialyzer membranes and various forms of dialysis have little effect on ADAMTS13 because of its huge molecular size [30].

Therefore, even though vWF concentrate has a positive effect on controlling bleeding in acquired von Willebrand syndrome (AvWS), it is neither ineffective nor inadequate in our study, so there is no need to employ it as a therapeutic option in our GI bleeding reported cases. However, in hemodialysis-dependent end-stage renal disease, vWF:RCo levels can be used as a diagnostic tool to predict gastrointestinal bleeding. And as a theoretical implication of our study, ADAMTS13, a deficiency or antibodies against it may be the cause of elevation of vWF plasma levels duo to accumulation of vWF without cleavage and removal. Thus, beside the cytokines, which increased in hemodialysis patients and activate procoagulant factors that elevate particular haemostatic factors levels including vWF.

Our study is limited and needs further confirmation duo to many factors, first one is a small number of cases. Second is missing follow up of the selected cases with serial vWF Ag levels and vWF:RCo values and its correlation especially with gastrointestinal bleeding cases. Third is a very small number of GI bleeding cases (only four cases).

CONCLUSION

Lower albumin levels and higher vWF-Ag levels and vWF:RCo values were positively correlated with increased risk of GIT bleeding. VWF:RCo values was an independent predictor for GIT bleeding in ESRD patients on hemodialysis. The study suggests no need for therapeutic use of vWF concentrate in treatment of GIT bleeding in adult hemodialysis-dependent ESRD and may be limited diagnostic value of vWF level & activity in GIT bleeding in adult hemodialysis-dependent ESRD.

RECOMMENDATIONS

The study suggests larger, longer-term studies with larger sample sizes and longer follow-ups are needed to provide accurate conclusions and control for confounding factors such as the differences between hemodialysis, plasmapheresis and peritoneal dialysis; where there is no use of anticoagulants nor dialyzers and also consider the differences between arteriovenous fistula and permacath for hemodialysis. Also, we need to detect the differences in outcome with concomitant diseases, which decrease vWF level as aortic stenosis, left ventricular assist devices and systemic lupus erythematosus and we need to explore if there is changes in results in cases received therapeutic oral anticoagulants. Also, we need to compare between CKD patients before dialysis and ESRD dialysis-dependent patients and renal transplant patients. It is very important to clarify the differences of different causes of GIT bleeding and its effect on vWF mainly between

AVMs, which is simulating arteriovenous shunt in hemodialysis and other GIT mucosal erosion causes that may get benefit from vWF concentrate if there have evidence of deficiency in these cases.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request .

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