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Short Report

Relationship between D-dimer Levels and the Glomerular Filtration Rate in Patients with Chronic Kidney Disease

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ABSTRACT

Background: Given the high sensitivity of the D-dimer assessment when ruling out pulmonary embolism, the present study was conducted to investigate the D-dimer levels in patients with CKD based on their related GFR. **Methods:** The present cross-sectional study included 98 patients with CKD who presented to the nephrology clinic of the Shahid Beheshti Hospital in Hamadan, Iran. The patients gave informed consent before enrollment. The data of each patient was recorded in the form of a checklist. The data analysis was performed using the SPSS software at a significance level of 0.05%. **Results:** There was found to be a negative correlation between GFR and D-dimer levels in the study participants. However, there was no evidence of thromboembolic events during the 1-year follow-up. Moreover, we found a direct relationship between patient age and the serum levels of the D-dimer, in that the D-dimer levels were higher in the participants who were older. **Conclusion:** We concluded that serum D-dimer level has a positive correlation with age, while it has a negative correlation with GFR in CKD patients. However, no evidence of thromboembolic events was found.

Key words: Chronic Renal Failure, D-dimer, Dialysis, Glomerular Filtration Rate

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INTRODUCTION

Chronic Kidney Disease (CKD) is defined as a structural defect or decreased function of the kidney [1]. This disorder is diagnosed by having at least one of the following criteria: a Glomerular Filtration Rate (GFR) of < 60 ml/min/ 1.73 m^2, albuminuria, disturbances in urinary sedimentation, histologic or imaging evidence of renal injury, renal tubular disorders, and a history of renal transplantation for longer than 3 months [2,3].

Glomerular filtration is the process in which the blood passes from a glomerular capillary tuft inside the Bowman's capsule where it is cleared of waste products. However, erythrocytes, leukocytes, and plasma proteins are exceptions, so they remain inside the vessel [4,5]. It has been shown that GFR gradually decreases with age. This reduction is affected by diet, muscular mass, gender, and race [6]. Based on the GFR, CKD is classified into 5 stages from mild to an advanced disease with End-Stage Renal Disease (ESRD) being the final stage. This is characterized by dramatically reduced GFR and a need for dialysis. In this stage, either peritoneal dialysis or hemodialysis is selected for the patient depending on their condition [7–11].

D-dimer, one of the molecules that results from fibrin degradation, is very low in the blood of healthy individuals. As an indicator of increased fibrinolysis, elevated levels of D-dimer indicate intravascular coagulation and thrombotic disease. Given its high sensitivity and negative predictive value, D-dimer testing is routinely used in clinical practice as a primary assessment for patients with suspected VTE [12,13]. A negative D-dimer test can definitely rule out VTE. Thus, there is no need for subsequent imaging and anticoagulant therapy [13,14]. Although D-dimer is almost always elevated in VTE, it can also increase due to several other conditions including acute illness, recent trauma or surgery, active malignancies, severe atherosclerosis, and pregnancy, leading to its relatively low specificity and positive predictive value [15]. Moreover, the specificity of D-dimer testing for the VTE diagnosis is even lower in patients with mild or moderate CKD. In these patients, the D-dimer level is associated with the CKD stage and disease progression [16], therefore positive D-dimer results have no definite diagnostic value for ESRD patients under hemodialysis [17] because they often have several other comorbidities such as atherosclerosis and malignancy which are also associated with increased serum D-dimer levels [18,19]. In addition, investigations have shown that the specificity of D-dimer testing for pulmonary embolism diagnosis is significantly reduced in CKD patients because the D-dimer levels are associated with the CKD stage [16]. Therefore, the present

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study aimed to investigate the serum D-dimer level and its relationship with GFR in patients with CKD.

METHODS

The present cross-sectional study included 98 patients with the diagnosis of CKD who presented to the nephrology clinic of Shahid Beheshti Hospital in Hamadan, Iran from April 2019 to February 2021. The exclusion criteria were active malignancy, rheumatoid arthritis, systemic lupus erythematosus, sickle cell anemia, current history of thromboembolic events, pregnancy, post-partum conditions, recent abdominal, thoracic or orthopedic surgery, cocaine use, hemoptysis, thrombophilia, and a history of trauma in the last 4 weeks. The present study was approved by the Ethics Committee of the Hamadan University of Medical Sciences with the ethics code of IR.UMSHA.REC.1398.869.

The participants gave informed written consent. They then gave blood samples, which were used to proceed with a quantitative D-dimer assessment using the ELFA VIDAS kits by the Biomerieux Company. The cut-off value was 500 ng/ml for a quantitative D-dimer assessment. The GFR of the participants was calculated using the MDRD formula and their serum creatinine levels, which were obtained from the recent test results of the patients. The patients were classified into 2 groups based on the calculated GFR as follows:

1. Moderate renal failure: $30 \leq GFR \leq 59$
2. Severe renal failure: $GFR \leq 29$

The clinical and demographic data of the participants, including age, gender, educational level, BMI, the cause of renal failure, serum creatinine, D-dimer level, GFR, and CKD duration were recorded in the related checklists.

Data analysis was performed using the SPSS-24 software with a significance level of 0.05%. The Pearson's correlation, Spearman's correlation, t-test, and Mann-Whitney U test were used in the analytical part of this study.

RESULTS

The present study investigated 98 patients diagnosed with CKD. According to our results, 52.04% of the participants were men. The mean ± SD of the participants' age was 58.14 ± 15.89 years with a range of 27 – 93. More than half of the patients were older than 60, and most of them were illiterate or had less than a high school diploma. Regarding BMI, 42.86% had a BMI of 18.5 - 25 kg/m^2 (**Table 1**). In total, 52 (53.06%) patients were undergoing hemodialysis. The most common cause of renal failure was hypertension (45.92%), followed by diabetes (22.45%) (**Table 2**).

The mean ± SD values of serum creatinine and D-dimer levels were 4.96 ± 3.34 mg/dl and 1614.28 ± 1917.39 ng/ml, respectively. Moreover, the mean ± SD value for GFR was 20.27 ± 15.32 ml/min.1.73 m^2. The mean ± SD for CKD duration was 10.36 ± 6.54. Finally, for a total 98 participants, 75 (76.53%) had a positive D-dimer test, while 23 (23.47%) had a negative test.

The serum D-dimer level had a significant positive correlation with creatinine and age ($P < 0.05$), while it had a significant negative correlation with GFR ($P < 0.05$). Moreover, there was a significant negative correlation between GFR and creatinine level (**Table 3**).

Using the Mann-Whitney U test, we found a significant difference between the patients with moderate ($30 \leq GFR \leq 59$) and severe ($GFR \leq 29$) CKD and the D-dimer levels (986.37 ± 943.68 vs. 1853.06 ± 2133.95, $P = 0.024$).

DISCUSSION

According to our results, there was a significant relationship between serum D-dimer level and the patients' GFR and age. We also found a negative correlation between GFR and serum D-dimer level. Patients with a lower GFR had higher D-dimer levels. In addition, there was a direct correlation between age and serum D-dimer level, meaning that an increased age led to higher D-dimer levels.

The present study is compatible with most similar studies[20–24]. For example, a study by Robert-Ebadi *et al.* on 1,625 participants found a more significant relationship between D-dimer level and GFR in patients whose possibility of pulmonary embolism had been ruled out compared to those with a diagnosis of pulmonary embolism[23]. In a study of 1305 participants, 169 participants (13%) were affected by pulmonary embolism, Linder *et al.* showed there to be a significant relationship between the calculated GFR and D-dimer level[21]. A study by Gubensek *et al.* on 167 participants undergoing chronic hemodialysis reported a mean D-dimer level of 966 ng/ml in these patients. Moreover, 75% of the patients had a positive D-dimer test (> 500 ng/ml), and the D-dimer levels were significantly correlated with the participants' age[25]. These results are compatible with our results.

According to a study by Xi *et al.* involving 1784 participants, the mean D-dimer levels were 291.5 mg/L, 995.5 mg/L, and 1901.5 mg/L in the patients with normal renal function, mild renal disease, and moderate renal disease, respectively. They found a significant relationship between D-dimer level and GFR[24].

Table 1: Demographicsof the patients diagnosed with CKD

Variable	Sub-groups	Frequency	Percentage (%)
Age group (year)	Younger than 45	19	19.39
	45 - 60	28	28.57
	Older than 60	51	52.04
Gender	Men	51	52.04
	Women	47	47.96
Educatioal level	Illiterate	34	34.69
	Lower than the high school	41	41.84
	High school and diploma	12	12.24
	Academic	11	11.22
BMI (kg/m^2)	BMI $\leq$ 18.5	3	3.06
	18.5 < BMI $\leq$ 25	42	42.86
	25 < BMI $\leq$ 30	34	34.69
	30 < BMI	19	19.39

Table 2: Frequency distribution of renal failure causes in patients with CKD

CKD cause	Frequency	Percentage (%)
Diabetes	22	22.45
Hypertension	45	45.92
Nephrolithiasis and other urologic disorders	12	12.24
Polycystic kidney disease	10	10.20
Glomerulonephritis	5	5.10
Collagen-vascular diseases	2	2.04
Cardiorenal diseases	2	2.04

Table 3: Relationships between the study variables in patients with CKD

		D-dimer	Creatinine	GFR	Age	CKD duration
D-dimer	R	1	-	-	-	-
	P-value					
Creatinine	R	0.1661	1	-	-	-
	P-value	0.1021				
GFR	R	-0.2975	-0.8234	1	-	-
	P-value	0.0029*	0.0000*			
Age	R	0.2096	-0.0973	-0.0100	1	-
	P-value	0.0383*	0.3403	0.9224		
CKD duration	R	0.1749	0.0540	-0.1398	0.0986	1
	P-value	0.0849	0.5975	0.1697	0.3338	

* P-value < 0.05

Huang *et al.* performed a study on 115 participants and found a significantly elevated D-dimer level in patients with CKD stages 3, 4, and 5 [20].

Mohammed and Khalil performed a study on 49 patients with CKD and found there to be no significant relationship between D-dimer level and the patients' GFR and age. They reported a significant correlation between D-dimer level and CKD duration [22].

The present study had some limitations. For example, our sample size was smaller than similar studies due to the limited financial resources. Moreover, some patients refused to participate due to the invasive sampling method used.

CONCLUSIONS

According to our results, there was a significant correlation between the serum D-dimer level and the patients' GFR and age in patients with CKD, including those affected by ESRD who underwent hemodialysis. Given the present study results, we recommend setting a GFR-adjusted cut-off for D-dimer testing in patients with GFR <60 ml/min.1.73 m^2 to reduce the number of false-positive results. The patients with CKD will be less exposed to imaging modalities with contrast which may lead to contrast-related nephropathy, exacerbating the current renal dysfunction of the patients.

ABBREVIATIONS

BMI: Body Mass Index
CKD: Chronic Kidney Disease
ESRD: End-Stage Renal Disease
GFR: Glomerular Filtration Rate
SD: Standard Deviation
VTE: Venous Thromboembolism

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AUTHOR'S CONTRIBUTIONS

VS, SK, and NAS developed the original idea and the protocol, abstracted, and prepared the manuscript. SK and VS participated in the study design and analyzed the data. VS, and NAS contributed to the data gathering. All authors read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

Data and materials used and/or analysed during the current study are available The data that support the findings of the study are available from the corresponding author in SPSS form upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the amended Declaration of Helsinki. Institutional review board approval was obtained from the ethics committees of Hamadan University of Medical Sciences (Ethics code: IR.UMSHA.REC.1398.869), and all participants provided written informed consent.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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