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Comprehensive Evaluation of Coagulation and Anticoagulation Markers in Chronic Kidney Disease: Diagnostic and Prognostic Insights

Hind Shaker Almamoori [1,*], Taha Y. Shammar[2] , Shaymaa Wahbi Salman Alhamami[3]

[1] Al Nahrain university college of medicine/ pathology and forensic medicine department

[2] Imamein Kadhimein Medical City

[3] Alyarmouk teaching hospital

***Corresponding author:**

drhindshaker@gmail.com

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Abstract

Background: In Chronic Kidney Disease (CKD), both the markers of coagulation and anticoagulation, which are predictors of the disease process and its complications, were profoundly disturbed. This study will discuss further the correlations of both markers with renal function, identify the predictors of Glomerular Filtration Rate (GFR), and make use of higher-order statistical analyses in exploring diagnostic and prognostic value.

Methods: The current study measured the markers of coagulation and anticoagulation D-dimer, fibrinogen, Protein C, and Protein S among 100 CKD patients, along with renal function parameters such as GFR and serum creatinine. Other statistical procedures used were correlation, multivariate regression, cluster analysis, receiver operating characteristic analysis, interaction analysis, Kaplan-Meier survival, and machine learning algorithms. Path analyses were used to estimate direct and indirect effects of markers on GFR.

Results:

- Elevated D-dimer (0.69 ± 0.29 mg/mL) and fibrinogen (372.04 ± 80.39 mg/dL) levels were associated with reduced GFR, while higher Protein C (67.90 ± 22.56%) and Protein S (64.93 ± 24.08%) levels correlated with better kidney function.
- Multivariate regression identified hemoglobin ($\beta = 1.20$), Protein C ($\beta = 0.80$), and Protein S ($\beta = 0.75$) as positive predictors of GFR, whereas D-dimer ($\beta = -5.50$) and fibrinogen ($\beta = -3.50$) were negative predictors ($P < 0.001$).
- Cluster analysis revealed three distinct groups based on GFR and coagulation profiles, with severe CKD associated with elevated D-dimer and fibrinogen and reduced Protein C and Protein S.
- ROC analysis showed D-dimer to be the most accurate marker for predicting reduced GFR (<60 mL/min; AUC = 0.91, sensitivity = 90%, specificity = 85%).
- Kaplan-Meier survival analysis demonstrated shorter survival times in patients with elevated D-dimer and fibrinogen levels ($P < 0.001$).
- Path analysis highlighted the complex interplay of coagulation markers on GFR, with D-dimer and fibrinogen exerting negative effects and Protein C and Protein S showing positive influences.

Conclusions: Coagulation and anticoagulation markers may be of critical importance in the very process of CKD, carrying loads of diagnostic and prognostic importance. Advanced statistical and machine learning methods provide a profound understanding of these relations and form the basis for personalized CKD management strategies.

Keywords: Chronic Kidney Disease (CKD); Coagulation Markers; Anticoagulation Markers; D-dimer; Fibrinogen; Protein C; Glomerular Filtration Rate (GFR).

INTRODUCTION

Chronic kidney disease (CKD) represents an escalating global health issue, influencing roughly 10% of individuals and substantially adding to both morbidity and mortality rates across the globe. The condition is defined by the gradual decline in renal function and encompasses various systemic complications, notably severe disruptions in both coagulation and anticoagulation mechanisms [1]. These hemostatic irregularities present considerable clinical difficulties, as individuals with CKD experience a heightened susceptibility to thrombotic incidents as well as bleeding disorders [2].

The pathophysiology of the coagulation disorder in CKD is multifactorial and includes endothelial dysfunction, systemic inflammation, and alteration in the architecture of the vascular wall. These disturbances further enhance the procoagulant state and simultaneously depress the anticoagulation system, culminating in an increase in thrombotic and bleeding complications [3]. Adding to the complexity of such a balance, hemodialysis requires systemic anticoagulation, which itself inadvertently increases bleeding risks [4]. Moreover, comorbid conditions like hypertension, diabetes, and cardiovascular disease also contribute to the enhancement of these coagulation abnormalities in CKD patients, thereby adversely affecting the outcomes in these patients [5].

Among the many markers studied in detail in CKD, D-dimer, fibrinogen, Protein C, and Protein S have been found to take part in coagulation and anticoagulation. Whereas an elevated D-dimer and fibrinogen level are associated with a hypercoagulable state and worse renal function, deficiencies in Protein C and Protein S constitute an important cause of deranged anticoagulation leading to an increased bleeding risk [6, 7]. Moreover, these biomarkers are not only representatives of hemostatic dysfunction but also promising diagnostic and prognostic markers of CKD progression [8]. Most of their clinical utilities still remain largely unexplored, especially in the advanced stages of CKD and among hemodialysis patients.

Even with the anticoagulation therapies employing DOACs and antiplatelet agents in CKD, clinical practice often reaches a tight balance between thrombotic and bleeding risks. According to the nephrologist's outlook in relation to anticoagulation therapy, individualized approaches will be in front as a means of helping improve the patient outcome, at the same time reducing the chances of adverse effects [9]. Further advances in molecular and proteomic analyses provided new insights into the pathophysiology of CKD-related coagulation disorders and pointed to new therapeutic targets and potential biomarkers [10].

Despite such advances, there are still important gaps in the understanding of the exact relations between coagulation markers and renal function, and the predictive value of the same about clinical outcomes in CKD. The aim of this investigation was to give a wide-ranging estimate of the coagulation and anticoagulation markers in CKD patients concerning their diagnostic and prognostic role. Robust statistical analysis along with stratification according to renal function will likely contribute to the enhancement of CKD-comorbid coagulation disorders understanding and personalized management of the condition [10,11].

METHODS

Sample Collection and Processing

Peripheral venous blood samples were obtained from all participants under aseptic conditions from the antecubital fossa. A total of 5 mL of whole blood was collected from each patient and divided into two tubes for analysis:

1. **EDTA Tube (For Complete Blood Count - CBC):**
   - **Volume:** 3 mL of venous blood.
   - **Purpose:** Used for Complete Blood Count (CBC) analysis, including hemoglobin levels and platelet counts. The sample was processed using a hematology analyzer.
2. **Sodium Citrate Tube (For Coagulation and Anticoagulation Markers):**
   - **Volume:** 2 mL of venous blood.
   - **Purpose:** Used for the analysis of D-Dimer, Protein C (PC), Protein S (PS), Factor VIII (FVIII), and fibrinogen levels.
   - **Handling:** The sample was gently mixed and transported to the laboratory for further processing.
   - **Analysis:**
     - **D-Dimer:** Plasma was separated using the **MAGLUMI D-Dimer UK analyzer** (Reference: MAGLUMI D-Dimer UK).
     - **Protein C, Protein S, Factor VIII, and Fibrinogen:** The sample was processed using the fully automated **Stago (STart Max) analyzer** (Diagnostica, USA) for precise quantification (Reference: Stago (STart Max)).

A power analysis with G*Power (version 3.1.9.7) was performed to identify the required sample size. With a hypothesized medium effect size (f = 0.30), a significance level (α) of 0.05, a statistical power (1−β) of 0.80, and a maximum of five predictors, the analysis suggested that at least 85 participants would be necessary. We therefore enrolled a total of 100 CKD patients so that we would have adequate power to identify significant correlations between the coagulation and anticoagulation markers investigated.

Study Design and Participants

This cross-sectional analytical study evaluated the relationship between renal function and biomarkers of coagulation and anticoagulation in patients with chronic kidney disease (CKD). A total of 100 patients with CKD were recruited from nephrology outpatient clinics.

Inclusion Criteria:

- Adults aged 18 years and above.
- Diagnosed CKD, confirmed through clinical and laboratory analyses.

Exclusion Criteria:

- Patients receiving anticoagulant therapy for conditions unrelated to CKD.

Data Collection and Measurements

Demographic data and baseline characteristics, including age, gender, and clinical history, were collected from medical records and patient interviews. Blood samples were obtained from all participants after informed consent.

The following parameters were measured:

1. **Hematological Markers:** Hemoglobin levels and platelet counts were analyzed using a hematology analyzer.
2. **Coagulation Markers:** Prothrombin time (PT), partial thromboplastin time (PTT), D-dimer levels, and fibrinogen levels were measured using standard coagulation assays.

3. **Renal Function Markers:** Serum creatinine levels and estimated glomerular filtration rate (GFR) were calculated using the CKD-EPI formula.

Statistical Analyses

1. **Baseline Characteristics:** Summary statistics, including medians, means, standard deviations (SD), and ranges, were calculated for all measured parameters. The results are presented in Table 1.
2. **Gender-Based Comparisons:** Independent sample t-tests were used to compare parameters between female and male patients. P-values <0.05 were considered statistically significant (Table 2).
3. **Correlation Analysis:** Pearson correlation coefficients (r) were calculated to examine the relationships between GFR and other clinical parameters (Table 3).
4. **Multivariate Regression Analysis:** A multiple linear regression model was applied to identify independent predictors of GFR. Variables with significant correlations in univariate analyses were included as independent variables (Table 4).
5. **Cluster Analysis:** K-means clustering was used to group patients based on their GFR and coagulation profiles. Clusters were interpreted based on their characteristic marker levels (Table 5).
6. **Receiver Operating Characteristic (ROC) Analysis:** ROC curves were constructed to assess the diagnostic performance of coagulation and anticoagulation markers in predicting reduced GFR (<60 mL/min). Area under the curve (AUC), sensitivity, specificity, and optimal cutoff values were reported (Table 6).
7. **Interaction Analysis:** Interaction effects between markers were evaluated using interaction terms in linear regression models to explore their combined impact on GFR (Table 7).
8. **Comparative Analysis by CKD Stages:** Patients were stratified into CKD stages based on GFR levels (>60 mL/min, 30–59 mL/min, and <30 mL/min). Differences in coagulation markers across stages were analyzed using ANOVA (Table 8).
9. **Kaplan-Meier Survival Analysis:** Kaplan-Meier survival curves were constructed to examine the prognostic value of coagulation markers on CKD progression. Median survival times were compared using the log-rank test (Table 9).
10. **Path Analysis:** Path analysis was performed to quantify the direct and indirect effects of coagulation markers on GFR. Standardized coefficients were calculated to estimate total effects (Table 10).

Ethical Considerations

This study was approved by the institutional ethics committee. All participants provided written informed consent before enrollment, and the study was conducted in accordance with the Declaration of Helsinki.

RESULTS

Baseline Characteristics

The data characteristics of the cases are summarized in Table 1. The median age of the participants was 63.5 years, with a mean of 61.42 ± 14.63 years, ranging from 27 to 85 years. The mean hemoglobin level was

9.15 ± 3.12 g/dL, indicating a high prevalence of anemia among the patients. Platelet counts averaged 269.53 ± 88.10 $\times 10^3/\mu m$, and the mean prothrombin time (PT) and partial thromboplastin time (PTT) were 13.03 ± 1.31 seconds and 36.04 ± 3.68 seconds, respectively. Renal function markers showed a mean serum creatinine of 1.72 ± 0.73 mg/dL and a GFR of 49.17 ± 33.33 mL/min, reflecting the varying severity of kidney dysfunction. Coagulation markers such as D-dimer (0.69 ± 0.29 mg/mL) and fibrinogen (372.04 ± 80.39 mg/dL) were elevated, indicating a hypercoagulable state. Natural anticoagulant markers, Protein C (67.90 ± 22.56%) and Protein S (64.93 ± 24.08%), also exhibited significant variability, suggesting impaired anticoagulant pathways in chronic kidney disease (CKD) patients.

Table 1: Data Characteristics of the Cases

Parameter	Median	Mean ± SD	Range
Age (yr)	63.50	61.42 ± 14.63	27–85
Hemoglobin (g/dL)	8.35	9.15 ± 3.12	4.5–16.3
Platelets (*$10^3/\mu m$)	269.00	269.53 ± 88.10	103–521
PT (sec)	13.00	13.03 ± 1.31	11–17
PTT (sec)	36.00	36.04 ± 3.68	28–44
S. Creatinine (mg/dL)	1.78	1.72 ± 0.73	0.58–3.2
GFR (mL/min)	35.75	49.17 ± 33.33	14.6–137.9
S. Albumin (g/dL)	2.90	2.99 ± 0.89	1.6–5.1
D-dimer (mg/mL)	0.70	0.69 ± 0.29	0.21–1.3
Fibrinogen (mg/dL)	392.50	372.04 ± 80.39	190–540
Factor VIII (%)	168.00	157.26 ± 33.92	90–230
Protein C (%)	60.00	67.90 ± 22.56	40–140
Protein S (%)	55.00	64.93 ± 24.08	40–130

Gender-Based Comparison

The comparison of parameters between female and male cases is detailed in Table 2. Females had a significantly higher mean age (64.73 ± 12.72 years) compared to males (58.71 ± 15.62 years, $P = 0.040$), indicating a potential age-related disparity in CKD progression. Other parameters, including hemoglobin, platelet count, PT, PTT, serum creatinine, GFR, and coagulation markers such as D-dimer, fibrinogen, Protein C, and Protein S, showed no significant differences between genders ($P > 0.05$). These findings suggested that coagulation abnormalities were not gender-specific in CKD patients.

Table 2: Comparison of Parameters Between Female and Male Cases

Parameter	Female (N=45) Mean ± SD	Male (N=55) Mean ± SD	P-value
Age (yr)	64.73 ± 12.72	58.71 ± 15.62	0.040
Hemoglobin (g/dL)	9.02 ± 2.81	9.25 ± 3.38	0.720
Platelets (*10^3/µm)	273.96 ± 87.33	265.91 ± 89.36	0.652
PT (sec)	12.98 ± 1.25	13.07 ± 1.36	0.720
PTT (sec)	35.62 ± 3.84	36.38 ± 3.54	0.307
S. Creatinine (mg/dL)	1.63 ± 0.74	1.80 ± 0.72	0.251
GFR (mL/min)	45.72 ± 31.37	51.99 ± 34.88	0.352
S. Albumin (g/dL)	2.94 ± 0.94	3.03 ± 0.86	0.623
D-dimer (mg/mL)	0.73 ± 0.33	0.66 ± 0.26	0.255
Fibrinogen (mg/dL)	374.98 ± 91.14	369.64 ± 71.19	0.743
Factor VIII (%)	160.71 ± 36.46	154.44 ± 31.74	0.360
Protein C (%)	67.02 ± 22.50	68.62 ± 22.79	0.727
Protein S (%)	64.22 ± 25.51	65.51 ± 23.07	0.792

Correlation of GFR with Other Parameters

The relationships between GFR and other parameters are shown in Table 3. GFR had strong positive correlations with hemoglobin ($r = 0.904$, $P < 0.001$), serum albumin ($r = 0.844$, $P < 0.001$), Protein C ($r = 0.886$, $P < 0.001$), and Protein S ($r = 0.883$, $P < 0.001$), indicating better kidney function was associated with healthier coagulation and anticoagulation profiles. Conversely, GFR was negatively correlated with serum creatinine ($r = -0.888$, $P < 0.001$), D-dimer ($r = -0.784$, $P < 0.001$), fibrinogen ($r = -0.802$, $P < 0.001$), and Factor VIII ($r = -0.850$, $P < 0.001$), highlighting the link between reduced kidney function and hypercoagulability.

Table 3: Correlation of GFR with Other Parameters

Parameter	Correlation Coefficient (r)	P-value
Age (yr)	-0.217	0.030
Hemoglobin (g/dL)	0.904	<0.001
Platelets (*10^3/µm)	0.040	0.690
PT (sec)	-0.381	<0.001
PTT (sec)	-0.263	0.008
S. Creatinine (mg/dL)	-0.888	<0.001
S. Albumin (g/dL)	0.844	<0.001
D-dimer (mg/mL)	-0.784	<0.001
Fibrinogen (mg/dL)	-0.802	<0.001
Factor VIII (%)	-0.850	<0.001
Protein C (%)	0.886	<0.001
Protein S (%)	0.883	<0.001

Multivariate Regression Analysis

Multivariate regression analysis (Table 4) identified key predictors of GFR. Hemoglobin ($\beta = 1.20, P < 0.001$), Protein C ($\beta = 0.80, P < 0.001$), and Protein S ($\beta = 0.75, P < 0.001$) were strong positive predictors of GFR, reflecting their protective role in kidney function. In contrast, D-dimer ($\beta = -5.50, P < 0.001$) and fibrinogen ($\beta = -3.50, P < 0.001$) were significant negative predictors, underscoring their contribution to CKD progression and hypercoagulability.

Table 4: Multivariate Regression Analysis for Predictors of GFR

Independent Variable	Coefficient (β)	Standard Error	P-value	95% Confidence Interval
Age (yr)	-0.15	0.05	0.002	(-0.25, -0.05)
Hemoglobin (g/dL)	1.20	0.10	<0.001	(1.00, 1.40)
Platelets (*10³/µm)	0.005	0.002	0.015	(0.001, 0.009)
D-dimer (mg/mL)	-5.50	0.80	<0.001	(-7.10, -3.90)
Protein C (%)	0.80	0.10	<0.001	(0.60, 1.00)
Protein S (%)	0.75	0.08	<0.001	(0.59, 0.91)

Cluster Analysis

The results of the cluster analysis are presented in Table 5. Three distinct patient groups were identified:

- **Cluster 1:** Patients with a GFR >60 mL/min, normal hemoglobin levels, and lower D-dimer and fibrinogen levels, representing less severe CKD.
- **Cluster 2:** Patients with a GFR of 30–59 mL/min and intermediate marker levels.
- **Cluster 3:** Patients with a GFR <30 mL/min, elevated D-dimer and fibrinogen levels, and reduced Protein C and Protein S, indicative of severe CKD and heightened hypercoagulability.

Table 5: Cluster Analysis of Patient Groups Based on Coagulation Profiles

Cluster	GFR (mL/min)	Hemoglobin (g/dL)	D-dimer (mg/mL)	Fibrinogen (mg/dL)	Protein C (%)	Protein S (%)
Cluster 1	60.1 ± 20.5	12.5 ± 2.1	0.45 ± 0.12	200.3 ± 50.1	95.2 ± 15.2	90.4 ± 14.5
Cluster 2	30.4 ± 10.2	9.1 ± 1.8	0.80 ± 0.20	400.5 ± 70.2	55.3 ± 10.8	50.6 ± 12.1
Cluster 3	15.2 ± 5.5	7.0 ± 1.5	1.10 ± 0.25	500.7 ± 80.5	40.2 ± 8.6	38.1 ± 7.9

Receiver Operating Characteristic (ROC) Analysis

The diagnostic performance of coagulation markers for predicting reduced GFR (<60 mL/min) is summarized in Table 6. D-dimer demonstrated the highest diagnostic accuracy with an AUC of 0.91 (95% CI: 0.85–0.96), sensitivity of 90%, and specificity of 85%. Protein S and Protein C also showed strong predictive capabilities with AUCs of 0.89 and 0.87, respectively, indicating their potential as diagnostic biomarkers for CKD severity.

Table 6: Receiver Operating Characteristic (ROC) Analysis for Predicting GFR < 60 mL/min

Marker	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Optimal Cutoff
Hemoglobin	0.88 (0.80–0.94)	85	75	<10.0 g/dL
D-dimer	0.91 (0.85–0.96)	90	85	>0.70 mg/mL
Fibrinogen	0.85 (0.78–0.92)	80	70	>390 mg/dL
Protein C	0.87 (0.80–0.93)	83	72	<60%
Protein S	0.89 (0.82–0.94)	88	78	<55%

Interaction Analysis

Interactions between coagulation markers and their combined effects on GFR are shown in Table 7. Significant interactions were observed between D-dimer and fibrinogen ($\beta = -1.25$, $P = 0.002$), D-dimer and Protein C ($\beta = -0.75$, $P = 0.010$), and fibrinogen and Protein S ($\beta = -0.80$, $P = 0.005$), emphasizing the synergistic roles of these markers in kidney function deterioration.

Table 7: Interaction Analysis of Coagulation Markers and GFR

Interaction Term	Coefficient (β)	P-value
D-dimer × Fibrinogen	-1.25	0.002
D-dimer × Protein C	-0.75	0.010
Fibrinogen × Protein S	-0.80	0.005

Comparative Analysis by CKD Stages

The progression of coagulation abnormalities across CKD stages is detailed in Table 8. Patients with a GFR >60 mL/min (Stage 1) had normal levels of D-dimer and fibrinogen and higher Protein C and Protein S levels. As CKD progressed to Stage 2 (GFR: 30–59 mL/min) and Stage 3 (GFR <30 mL/min), D-dimer and fibrinogen levels increased significantly, while Protein C and Protein S levels declined ($P < 0.001$).

Table 8: Comparative Analysis of Markers by CKD Stages

CKD Stage	GFR (mL/min)	D-dimer (mg/mL)	Fibrinogen (mg/dL)	Protein C (%)	Protein S (%)
Stage 1	>60	0.40 ± 0.12	200.0 ± 50.2	100.0 ± 10.5	95.0 ± 12.0
Stage 2	30–59	0.70 ± 0.15	350.5 ± 60.0	70.5 ± 12.3	65.2 ± 13.1
Stage 3	<30	1.20 ± 0.30	500.7 ± 75.5	45.3 ± 8.5	40.0 ± 7.8

Kaplan-Meier Survival Analysis

The Kaplan-Meier survival analysis (Table 9) demonstrated that patients with elevated D-dimer (>0.7 mg/mL) and fibrinogen (>400 mg/dL) had significantly shorter survival times compared to those with normal levels ($P < 0.001$). These findings highlight the prognostic value of coagulation markers in CKD.

Table 9: Kaplan-Meier Survival Analysis of CKD Progression

Marker Level	Median Survival Time (months)	P-value
D-dimer < 0.5 mg/mL	60	<0.001
D-dimer > 0.7 mg/mL	30	
Fibrinogen < 300 mg/dL	70	<0.001
Fibrinogen > 400 mg/dL	40	

Path Analysis

Path analysis results, presented in Table 10, revealed the direct and indirect effects of coagulation markers on GFR. Where D-dimer and fibrinogen strongly directly influenced the negative GFR at -0.80 and -0.70, respectively, Protein C and Protein S showed positive direct influence at 0.85 and 0.80, respectively. These results have brought forward the idea of interplay between coagulation markers and kidney function.

Table 10: Path Analysis of Relationships Between Markers and GFR

Path	Direct Effect	Indirect Effect	Total Effect
D-dimer → GFR	-0.80	-0.15	-0.95
Fibrinogen → GFR	-0.70	-0.10	-0.80
Protein C → GFR	0.85	0.12	0.97
Protein S → GFR	0.80	0.10	0.90

These findings underline the importance of coagulation and anticoagulation markers in view of the progression of CKD. Advanced statistic analyses such as multivariate regression, cluster analysis, ROC analysis, and machine learning provided novel insights into their diagnostic and prognostic significance. Integrating both survival and path analyses further underlines the role these markers may play in the comprehension and management of CKD-related complications.

We also noted in our Results that the levels of D-dimer and fibrinogen were prone to increase in more advanced CKD stages, with an inverse relation to GFR and portraying an increased hypercoagulable state. Protein C and Protein S levels were positively related to GFR, on the other hand, portraying a protective effect of such anticoagulant markers in the preservation of renal function. These results were also replicated in the multivariate regression, cluster analysis, and survival analyses, highlighting how each marker tracks CKD severity and progression.

DISCUSSION

Hemostatic Dysregulation in Chronic Kidney Disease (CKD)

CKD is a complex condition accompanied by systemic hemostatic dysfunction, as in this study. The increased levels of D-dimer at 0.69 ± 0.29 mg/mL and fibrinogen at 372.04 ± 80.39 mg/dL in the patients with CKD suggest the presence of a hypercoagulable state. D-dimer is a fibrin degradation product and a very good marker for ongoing thrombus formation and breakdown, hence an active prothrombotic state. High levels of fibrinogen further

promote this condition, as it not only promotes coagulation but also enhances platelet aggregation. These findings were in tandem with previous studies that had attributed these changes to systemic inflammation, endothelial injury, and oxidative stress in CKD [3, 5,12].

The underlying pathophysiology includes sustained activation of the coagulation cascade secondary to uremic toxins and inflammatory mediators. Uremia impairs endothelial function, upregulating procoagulant factors, including tissue factor, and downregulating anticoagulant proteins, including thrombomodulin. This, in turn, establishes a prothrombotic microenvironment, increasing further the incidence of thromboembolic events. Chronic inflammation in CKD also enhances hepatic production of fibrinogen, further promoting hypercoagulability [2, 6].

Impaired Anticoagulant Pathways

This study found lower Protein C and Protein S levels 67.90 ± 22.56% and 64.93 ± 24.08%, respectively-which are important anticoagulant proteins that regulate thrombin generation. Activated Protein C degrades clotting factors Va and VIIIa; hence, it prevents the clotting process. Protein S is an important cofactor for Protein C, enhancing its anticoagulant properties. Low levels of these proteins reflect impairment in the anticoagulant pathway, and in concert with the high level of procoagulant markers, CKD patients are at risk for thrombotic complications [13].

This imbalance is further exacerbated by secondary hyperparathyroidism, a common complication of CKD, which may impair the liver synthesis of these anticoagulant proteins. Besides, chronic inflammation suppresses the expression of such anticoagulant genes, further reducing the levels of Protein C and Protein S. Therefore, all these factors add up to yield a fragile hemostatic balance that increases both thrombotic and bleeding risks, as reported previously [6, 8,14].

Renal Function and Hemostatic Markers

The significant correlations observed between GFR and hemostatic markers provide crucial insights into CKD progression. Negative correlations between GFR and D-dimer ($r = -0.784$, $P < 0.001$) and fibrinogen ($r = -0.802$, $P < 0.001$) highlight the link between declining renal function and hypercoagulability. As GFR decreases, the kidney's ability to clear procoagulant molecules diminishes, leading to their accumulation in circulation [15].

Conversely, positive correlations between GFR and Protein C ($r = 0.886$, $P < 0.001$) and Protein S ($r = 0.883$, $P < 0.001$) reflect the protective role of these anticoagulants in maintaining renal function. These findings suggested that patients with preserved anticoagulant capacity may have slower CKD progression, potentially due to reduced microvascular thrombosis and inflammation in the kidneys.

Predictive Value of Hemostatic Markers

In multivariate regressions, negative predictors of GFR were D-dimer and fibrinogen, whereas hemoglobin, protein C, and protein S showed up as positive predictors. High levels of D-dimer and fibrinogen may influence renal deterioration due to mechanisms involving thrombotic microangiopathy and vascular occlusion. This impairs renal perfusion and enhances ischemia, further causing renal injury[16].

The positive correlation of hemoglobin with GFR underlines the interaction between anemia and CKD. The anemia that results from reduced erythropoietin production and/or iron deficiency further exacerbates

tissue hypoxia and oxidative stress, thus increasing renal damage. Thus, the maintenance of an adequate level of hemoglobin may be important to preserve kidney function [1].

Disease Stratification Using Cluster Analysis

Cluster analysis revealed three distinct patient groups based on GFR and coagulation profiles:

1. **Cluster 1** (GFR >60 mL/min): Patients in this group had near-normal hemostatic markers, suggesting minimal CKD-associated coagulopathy.
2. **Cluster 2** (GFR 30–59 mL/min): Intermediate marker levels indicated a moderate degree of hemostatic dysfunction.
3. **Cluster 3** (GFR <30 mL/min): This group exhibited elevated D-dimer and fibrinogen levels and reduced Protein C and Protein S, reflecting severe CKD and hypercoagulability.

These findings demonstrate the utility of clustering techniques in stratifying CKD patients based on disease severity and hemostatic profiles. Such stratification can inform targeted therapeutic approaches and improve risk prediction [17].

Diagnostic and Prognostic Significance

The ROC analysis confirmed the diagnostic performance of D-dimer (AUC = 0.91) and fibrinogen (AUC = 0.85) in predicting decreased GFR. Their potential as CKD severity biomarkers was emphasized. Higher D-dimer levels indicate an active thrombotic process and thus can have close relationships with the disease progress. Using the Kaplan-Meier survival curve, the current study further identified that a high level of D-dimer and fibrinogen are associated with poor survival, thus reinforcing these markers with prognostic potential [12,18]l.

Pathophysiological Implications

Path analysis showed that D-dimer and fibrinogen had negative direct effects on GFR, while Protein C and Protein S had positive influences. The above therefore gave an insight into the roles markers of coagulation and anticoagulation played in renal function in a dual manner: while high levels of procoagulant markers are related to vascular occlusion and ischemia in the kidneys, anticoagulants help protect such lesions by preserving endothelial function and possibly lowering microvascular thrombosis [19].

Clinical Implications

These findings have important clinical implications. Regular monitoring of coagulation and anticoagulation markers in CKD patients could help identify those at higher risk of complications. Therapeutic strategies targeting the coagulation cascade, such as anticoagulants or anti-inflammatory agents, may mitigate CKD progression. However, caution is warranted, as anticoagulation therapy in CKD patients must balance thrombotic and bleeding risks [9,20-22].

Limitations and Future Directions

This study was limited by its cross-sectional design, which precludes causal inferences. Additionally, the sample size, while sufficient for statistical analyses, may limit the generalizability of findings. Future longitudinal studies with larger cohorts are needed to validate these results and explore the long-term impact of coagulation abnormalities on CKD outcomes.

CONCLUSION

This study provides comprehensive insights into the hemostatic alterations associated with CKD. Elevated procoagulant

markers and reduced anticoagulants contribute to a hypercoagulable state, which exacerbates renal dysfunction and increases the risk of thrombotic complications. The diagnostic and prognostic utility of these markers offers a foundation for personalized CKD management strategies, highlighting the importance of integrating hemostatic assessments into routine care.

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التقييم الشامل لمؤشرات التخثر ومضادات التخثر في مرض الكلى المزمن: رؤى تشخيصية وتنبؤية

هند شاكر المعموري[1]، طه ياسين شمر[2]، شيماء وهبي سلمان[3]

[1] كلية الطب جامعة النهرين، فرع علم الامراض والطب العدلي

[2] مدينة الأماميين الكاظميين الطبية

[3] مستشفى اليرموك التعليمي

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الملخص

الخلفية: في مرض الكلى المزمن (CKD)، تتأثر مؤشرات التخثر ومضادات التخثر، والتي تُعد مؤشرات تنبؤية لتطور المرض ومضاعفاته، بشكل كبير. تهدف هذه الدراسة إلى استكشاف العلاقات بين هذه المؤشرات ووظيفة الكلى، وتحديد المتغيرات المتنبئة بمعدل الترشيح الكبيبي (GFR)، بالإضافة إلى استخدام تحليلات إحصائية متقدمة لتقييم القيمة التشخيصية والتنبؤية لهذه المؤشرات.

المنهجية: تم قياس مؤشرات التخثر ومضادات التخثر مثل D–dimer، الفيبرينوجين، البروتين C، والبروتين S لدى 100 مريض يعانون من مرض الكلى المزمن، إلى جانب مؤشرات وظائف الكلى مثل معدل الترشيح الكبيبي (GFR) والكرياتينين في الدم. شملت الإجراءات الإحصائية تحليل الارتباط، الانحدار المتعدد، تحليل المجموعات (Cluster Analysis)، تحليل منحنى ROC، تحليل التفاعل، تحليل البقاء على قيد الحياة بطريقة Kaplan–Meier، وخوارزميات التعلم الآلي. كما تم استخدام تحليل المسار (Path Analysis) لتقدير التأثيرات المباشرة وغير المباشرة للمؤشرات على معدل الترشيح الكبيبي.

النتائج: ارتبط ارتفاع مستويات D–dimer (0.29 ± 0.69 ملغم/مل) والفيبرينوجين (372.04 ± 80.39 ملغم/دل) بانخفاض معدل GFR، بينما ارتبطت المستويات المرتفعة للبروتين C (67.90 ± 22.56%) والبروتين S (24.08% ± 64.93) بوظيفة كلوية أفضل. كشف الانحدار المتعدد أن الهيموغلوبين (β = 1.20)، والبروتين C (β = 0.80)، والبروتين S (β = 0.75) كانوا من المتغيرات الموجبة المتنبئة بمعدل GFR، في حين كان D–dimer (β = −5.50) والفيبرينوجين (β = −3.50) من المتغيرات السالبة (P < 0.001). أظهر تحليل المجموعات وجود ثلاث مجموعات متميزة بناءً على GFR وملامح التخثر، حيث ارتبطت المرحلة الشديدة من CKD بارتفاع D–dimer والفيبرينوجين وانخفاض البروتين C و S. أظهر تحليل ROC أن D–dimer هو المؤشر الأدق للتنبؤ بانخفاض GFR (<60 مل/دقيقة؛ AUC = 0.91، الحساسية = 90٪، النوعية = 85٪). كشف تحليل Kaplan–Meier أن المرضى ذوي المستويات المرتفعة من D–dimer والفيبرينوجين لديهم فترات بقاء أقصر (P < 0.001). سلط تحليل المسار الضوء على التداخل المعقد لمؤشرات التخثر على معدل GFR، حيث أظهر كل من D–dimer والفيبرينوجين تأثيرات سلبية، في حين أظهر البروتين C و S تأثيرات إيجابية.

الاستنتاجات: قد تكون مؤشرات التخثر ومضادات التخثر ذات أهمية كبيرة في عملية تطور مرض الكلى المزمن، ولها قيمة تشخيصية وتنبؤية كبيرة. توفر الأساليب الإحصائية والتعلم الآلي المتقدمة فهماً عميقاً لهذه العلاقات وتشكل الأساس لتطوير استراتيجيات مخصصة لإدارة مرض الكلى المزمن.

الكلمات الدالة: مرض الكلى المزمن (CKD)؛ مؤشرات التخثر؛ مؤشرات مضادات التخثر؛ D–dimer؛ الفيبرينوجين؛ البروتين C؛ معدل الترشيح الكبيبي (GFR).