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Original Research Article

Association of D-dimer with estimated glomerular filtration rate in chronic kidney disease at different stages in Indian population

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ABSTRACT

Background: Hyper-coagulability followed by cardiovascular disease is the most common cause of mortality in CKD (chronic kidney disease). Diagnostic usefulness of hypercoagulability marker at various stages of CKD needs to be assessed.
Study Design: An observational cross-sectional study.
Place and Duration of Study: Dept of Biochemistry, Institute of Nephrourology, Bangalore, India from January 2022 to March 2022.
Methodology: Study population consists of CKD patients attending Nephrology outpatient for follow up. They were categorized into 5 stages using eGFR values. Laboratory test including D-Dimer was assayed in all the participants using Abbott Architect ci4100 analyzer.
Results: In our study, a peaked and statistically significant (P value = <0.0001) D-Dimer values were observed in stage 4&5 (5.4 ±2.5) in comparison with stage 1, 2 & 3 (0.9±0.2). D- Dimer had strong negative correlation (R= - 0.79) with eGFR in stage 5 CKD.
Conclusion: D-Dimer assay should be considered as a part of routine investigations in CKD patients especially in developing countries like India, where most of the patients reach hospital only at the later stages of the disease, in order to achieve a better follow-up and management of the disease.

1. Introduction

Chronic kidney disease (CKD) has been recognized as a leading public health problem and has emerged as one of the leading non-communicable causes of death worldwide. It is a progressive condition that affects >10% of the general population worldwide, amounting to >800 million individuals.[1]

Evidence shows that CKD is a pathological condition of enduring inflammation and hypercoagulability and in its more progressive stages, that is, end-stage renal disease (ESRD),patients face a prothrombotic inclination and, in several instances, a bleeding diathesis. Renal dysfunction increases risk of thrombosis and hemorrhage, and falsely affects some of the coagulation factors, which are currently utilized to assess thrombosis risk. The precise etiology behind these haemostatic imbalances is barely investigated.[2]

D-Dimer is a generic term referring to multiple peptide fragments deriving from plasmin-mediated degradation of cross-linked fibrin. It is a classic hypercoagulability biomarker, useful in the diagnosis of thromboembolic events. Its presence reflects concomitant activation of both coagulation and fibrinolysis.[3]

There is an association between D-Dimer levels with the development of atherothrombosis and cardiovascular complications in patients with diabetes, indicating that D-Dimer can be useful in evaluating the risk of cardiovascular

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disease in these patients. D-Dimer levels also increase with the progression of renal disease in patients with diabetes, indicating that hypercoagulability could be a link between diabetic kidney disease and the increased risk of cardiovascular outcomes.[4]

Though the D-Dimer level is increased in patients with renal impairment, whether its diagnostic usefulness is maintained in these patients is not well determined especially in Indian population. Hence in the present study we aimed to evaluate the effects of renal impairment on diagnostic performances of D-Dimer for a better insight in CKD.

2. Methodology

This was a retrospective cross sectional study conducted in the Institute of Nephrourology, Bangalore, a tertiary care Centre for Nephro and urology care. Data was collected from the medical records and laboratory records of patients over a period of 3 months from January 2022 to March 2022.

2.1. Inclusion criteria

Adult patients both men and women of age group 20-60 year, diagnosed with CKD, attending routine nephrology outpatient department for follow- were randomly selected and enrolled for the study.

2.2. Exclusion criteria

CKD patients, with a preexisting history of venous thromboembolism, or on anticoagulants.

The CKD patients were further categorized into 5 groups based on the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines,[5] using eGFR (estimated glomerular filtration rate) values:

1. Stage 1: Kidney damage with normal or increased GFR (>90 mL/min/1.73 m^2)
2. Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m^2)
3. Stage 3a: Moderate reduction in GFR (45-59 mL/min/1.73 m^2)
4. Stage 3b: Moderate reduction in GFR (30-44 mL/min/1.73 m^2)
5. Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m^2)
6. Stage 5: Kidney failure (GFR < 15 mL/min/1.73 m^2 or dialysis)

Baseline demographics, clinical history of the patients along with routine biochemical parameters including D-Dimer were analyzed. eGFR was calculated by the CKD Epidemiology Collaboration (CKD-EPI) equation.[6]

2.3. Assays

Analysis of samples was done by Abbott ci4100 integrated autoanalyser in biochemistry laboratory. Ready to use kits from Abbott architect c systems were used for the analyses.

Urea by colorimetric method using urease method and creatinine using alkaline picrate method.

D-Dimer was assayed using plasma sample by Immunoturbidimetric method with reportable range of 0.5 -8.5 mg/L.

D-Dimer Assay is based on a latex enhanced immunoturbidimetric assay. D-Dimer proteins in the sample bind to the specific anti-D-Dimer antibody, which is coated on latex particles, and causes agglutination. The degree of the turbidity caused by agglutination can be measured optically and is proportional to the amount of D-Dimer in the sample.

2.4. Statistical analysis

Data were analyzed by Statistical Package for Social Science (SPSS) version 17. Results were presented as mean ±Standard Deviation (SD) for quantitative variables. The significance level, or p-value, was calculated using the unpaired t-test. A P value <0.005 was considered significant.

The correlation between D- dimer and inflammatory markers was done using Pearson correlation test. Pearson correlation coefficient(r) ranging -1 to +1 is considered to assess the correlation.

3. Results

We enrolled a total of 80 patients with CKD, into the study. Patients were categorized into 5 stages of CKD using eGFR values as per KDOQI guidelines, mentioned above. Biochemical data of the patients enrolled in the study are listed in (Table 1).

Among total CKD patients(n=80), 30 patients (37%) were in stage 5, 18 patients (22%) were in stage 4, 16 patients (20%) were in stage 3, 12 patients (15%) were in stage 2 and 4 patients (5%) were in stage 1 of CKD (Figure 1). D-Dimer levels were higher in stage 5 CKD patients followed by stage 4, 3, 2 and 1 (Figure 2).

CKD patients were further divided into 2 groups for the purpose of comparison. Group 1 included patients from stage 1, 2, 3 of CKD and Group 2 with stage 4 and 5. On comparison D-Dimer was significantly increased in group 2 compared to group 1 with p value (<0.0001) at 95% confidence interval (Table 2).

Pearson correlation study was done to assess the correlation between D-Dimer levels and eGFR levels in stage 5 CKD patients. We found that D Dimer levels had strong negative correlation (R= - 0.702) with e GFR values in stage 5 CKD patients which was significant.(p = 0.0009).(Table 3, Figure 3)

Table 1: Clinical and Biochemical data

Parameters	**Stage 1 CKD** (eGFR 15-30) **n=4**	**Stage 2 CKD** (eGFR 60-90) **n=12**	**Stage3 CKD** (eGFR 30- 60) **n=16**	**Stage 4 CKD** (eGFR 60-90) **n=18**	**Stag 5 CKD** (eGFR >90) **n=30**
Age(yrs)	49±13	46±15	45±17	41±10	42±12
Urea (10-44mg/dL)	30.96±9.6	46±5.1	83±24	130±40	168±70
Creatinine (0.57-1.1mg/dL)	0.9±0.1	1.5±0.2	2.4±0.1	4.1±0.1	12±5
D-Dimer < 0.5 mg/L	0.5±0.1	0.8±0.2	1.5±0.4	3.4±2.1	7.4±2.5
eGFR	96±3	65±2	38±6	19±4	5±2

Table 2: Comparison of D- Dimer levels in CKD patients

Parameter	**Group 1 (Stage 1 2 & 3) n=32**	**Group 2 (Stage 4 & 5) n=48**	**P value**	**Std error**
D-Dimer	0.9±0.2	5.4 ±2.5	P < 0.0001	0.444

Table 3: Correlation between D-Dimer and eGFR in stage 5 CKD

Stage 5 CKD	**D-Dimer**	**eGFR**	**Pearson correlation**	**P value**
	7.4±2.5	5±2	**R= - 0.79**	<0.0009

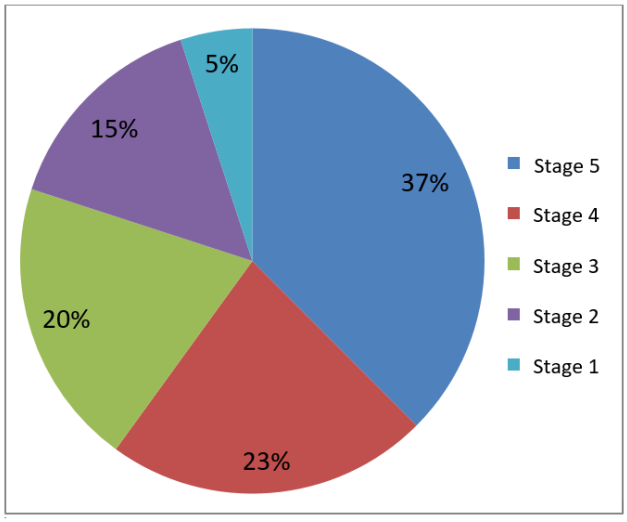

Fig. 1: Pie diagram showing distribution of CKD patients

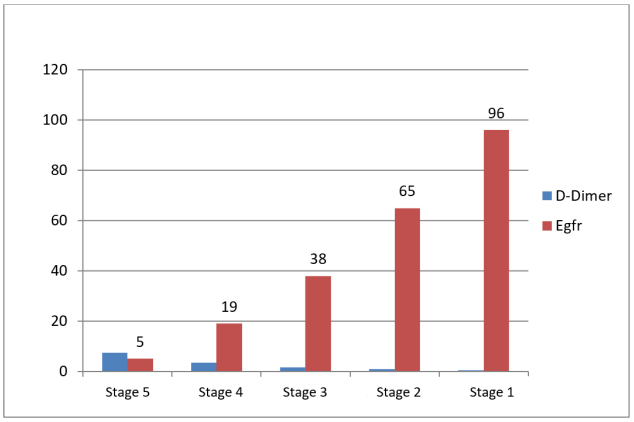

Fig. 2: Mean D-Dimer and eGFR values in 5 stages of CKD

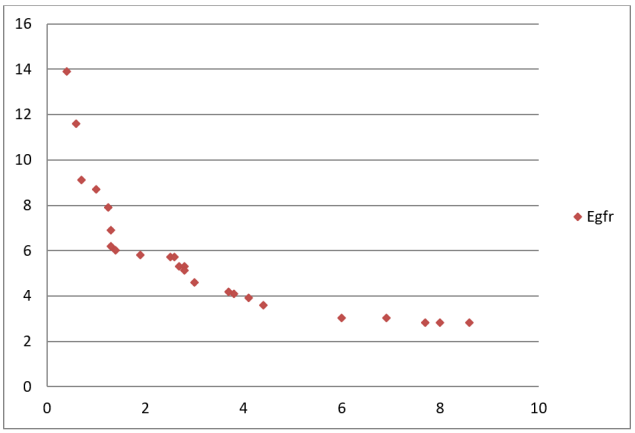

Fig. 3: Correlation between D-Dimer & eGFR

4. Discussion

Chronic kidney disease is hypercoagulable state in moderate and severe stage of the disease.[7] Patients with CKD present with variety of manifestations related to blood circulation like a state of increased coagulation[8] and increased fibrinolysis,[9] dysfunction of endothelium[10] and of platelets,[11] altogether manifested by both bleeding and thrombotic complications, as well as the development of cardiovascular disease, atherosclerosis and dyslipidaemia.[12]

In the present study we were able to show that D-Dimer levels which are the most specific markers of

hypercoagulable state was significantly elevated in CKD patients with later stage compared to those of earlier stage. Also, there was negative correlation of D-Dimer levels with eGFR indicating that patients with very low eGFR values are at very high risk of thrombotic complications.

The results from our study are in accordance with those of few similar studies across the world.[13–15] Xi et al. had done a similar study in 2016, involving the highest number of participants, i.e. 1784 CKD patients, where in they found that D-Dimer levels were high in later stages of CKD patients compared to earlier stages and also in old patients compared to younger ones.[14] In another study Linder et al. with 1305 participants with CKD, 169 participants (13%) were affected by pulmonary embolism, and D-Dimer levels were found be significantly elevated in these patients.[15]

Ours is the first study carried out in Indian population where in the association of D-Dimer with eGFR in different stages of CKD is studied thoroughly.

In a developing country like India, early diagnosis CKD is rare as most of the patients reach hospitals in later stages of the disease. Hence, it's very important that D-Dimer level should become a part of routine investigations in all CKD patients, in order to prevent them from developing cardiovascular complications.

5. Conclusion

A negative correlation between D-Dimer and eGFR suggests that D-Dimer should be the continuous marker of hypercoagulability in all CKD patients with eGFR <60 ml/min. The study also indicates the presence a high risk of venous thromboembolism and thus the cardiovascular disease in later stages of CKD. Hence, an age adjusted and an eGFR adjusted thresholds of D- Dimer levels should be established for routine care of CKD patients in order to achieve a better follow up and management of these patients.

6. Source of Funding

None.

7. Conflict of Interest

None.

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