DOI: 10.2478/cipms-2022-0019 Curr. Issues Pharm. Med. Sci., Vol. 35, No. 3, Pages 99-105

Current Issues in Pharmacy and Medical Sciences
Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA

journal homepage: http://www.curipms.umlub.pl/

Role of predictable biomarkers in early detection of cardiovascular events in Chronic Kidney Disease III and IV

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ARTICLE INFO

Received 12 December 2021
Accepted 8 February 2022

Keywords:
biomarkers,
cardiovascular disease,
chronic kidney disease,
C-reactive protein,
eGFR,
serum creatinine.

ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death in hemodialysis patients. This comes about because of a lack of predicted biomarkers in the risk analysis of CVD events in chronic kidney disease (CKD) patients. The present study aimed to determine the clinical utility of independent, predictable biomarkers such as serum creatinine, estimated Glomerular Filtration Rate (eGFR), high sensitive C-Reactive protein (hsCRP), fibrinogen and lipid profile as early predictors of CVD in CKD at stage III/IV.

Methods. This is a case-control study that includes a sample size of 100 patients of cases and 100 patients of controls who were recruited from November 2020 to April 2021, from the Nephrology department of the Visakhapatnam tertiary care teaching hospital, and present with chronic kidney disease – stage III/IV. The subjects' general conditions (age, gender, height, weight, systolic blood pressure, diastolic blood pressure, and smoking history); underlying diseases (coronary heart disease and diabetes mellitus) were recorded. Fasting venous blood samples were collected under aseptic conditions from the study group after taking informed consent. The measurement of serum creatinine was performed by modification of kinetic Jaffe reaction. The Cockcroft-Gault equation was used to calculate eGFR in both cases and controls. CRP testing was done with a Cobas C311 analyzer, using immunoturbidimetric assay. The Fibroquant kit from Tulip was employed to measure fibrinogen levels in blood samples, and enzymatic methods were applied for lipid profile analysis.

Results. In this study, higher mean values of hsCRP (34.28 mg/dl), increased serum creatinine levels (2.876 mg/dl), reduced eGFR (28.37 mls/min), high levels of serum fibrinogen (291.6 mg/dl), and cholesterol (214.5 mg/dl), HDL (28.34 mg/dl), TG (162.1 mg/dl), VLDL (32.41 mg/dl) and LDL (153.77 mg/dl) were found to be independent predictors of assessment of CV events in patients with CKD stages III and IV as determined by Chi-square test.

Conclusion. A prompt and accurate assessment of cardiovascular risk in CKD patients would enable more aggressive and focused treatment of the individuals who are most in need of preventive interventions to decrease incident rates.

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INTRODUCTION

Chronic kidney disease (CKD) is a term used to describe the worsening of kidney function over time. CKD is a significant contributing factor to the non-communicable disease burden in mortality and morbidity. In India, it should be aggressively tackled to reach the International Sustainable Development goal of reducing non-communicable disease premature mortality by a third by 2030. The prevalence of CKD in the Indian population varies considerably, and it is estimated to be around 785 per million [1]. Due to the lack of a renal registry in India, the exact extent of CKD/end state renal disease (ESRD) is unknown. Two community-based investigations found a prevalence of chronic renal failure of 0.16% and 0.79%, respectively, despite methodological differences.

The development of chronic kidney disease to end-stage renal disease is increasing due to an increase in diabetes mellitus, hypertension, obesity and an aging population ESRD. Many attempts to limit progression risks, such as lifestyle improvements and blood pressure management, often reduce cardiovascular risk. Cardiovascular disease (CVD) is the leading cause of death in haemodialysis patients, regardless of the reason. The estimated glomerular filtration rate (eGFR) of less than 70 mL/min/1.73 m^2 is related with a 68 percent increase in the risk of mortality from any cause, and a 51 percent increase in the risk of death from CVD, according to the Second National Health and Nutrition Examination Survey (NHANES II) [2]. Moreover, an eGFR of 15-59 mL/min/1.73 m^2 at baseline is linked with a 38 percent increase in the risk of CVD in the Atherosclerosis Risk in Communities research [3]. CVD tends to be the leading cause of death in more than 20% of the entire population with CKD every year, of which only half show evidence of dyslipidaemia. As a result, there is a need to identify additional cardiovascular disease risk factors.

One of the most promising predicted biomarkers in the risk analysis of CKD is high-sensitivity C-reactive protein (hs-CRP), which was one of the unique biochemical indicators studied in [4]. Although researches have shown a link between CRP and atherosclerotic artery disease, as well as acute cardiovascular events (including heart attacks and stroke in CKD patients), the impact of hsCRP has not been well investigated. In the general population, fibrinogen is a well-established predictor of CVD. Fibrinogen has been linked to the coagulation cascade, as well as cardiovascular problems [5-7]. As a result, the current study is critical for discovering new therapeutic techniques and diagnosing sick individuals early, in addition to correctly monitoring medicines.

Biomarkers for cardiovascular events (CVE) in CKD patients are subject to current research and may have the potential to reduce costs and extend symptom-free intervals through effective therapy control. The study aimed to determine the clinical utility of independent non-traditional predictable biomarkers such as serum creatinine, eGFR, hsCRP, fibrinogen, and lipid profile as early predictors of CAD in CKD at stage III/IV.

MATERIALS AND METHODS

Materials

Study design. This study is a case-control study.

Study population and sample size. Our research involved a sample size of one hundred patients of cases and one hundred patients of controls who were recruited from the Nephrology department and who presented chronic kidney disease – stage III/IV. The work was conducted in the Visakhapatnam tertiary care teaching hospital, from November 2020 to April 2021. All the study subjects were non-dialysis patients with chronic kidney disease.

Patients

Inclusion criteria

This includes patients with estimated GFR (eGFR) < 60 ml/min/1.73 m^2 for ≥3 months, while age-matched individuals without chronic kidney disease were selected in the control group. The patients were in the age group of 30-60 years and included both males and females with CKD stage III & IV.

Exclusion Criteria

Patients with renal disease caused by lupus nephritis or antineutrophil cytoplasmic autoantibody-associated vasculitis, patients with Nephrotic syndrome, patients with signs of acute infection, patients with a recent history of liver failure, trauma, surgery, cancer, or pregnancy, and patients on glucocorticoids, immunosuppressant, or anticoagulant medication in the previous month were all excluded. Patients with a history of previous thromboembolic or hemorrhagic episodes within the previous 12 months, as well as a history of cardiovascular disease, were also excluded.

Ethics approval

Institutional Ethics Committee clearance approval (No.GIMSR/Admn./Ethics/approval/IEC-10/2020) was obtained before the start of the study. Each participant were explained the details of the study, and informed consent was obtained.

Methodology

The subjects' general conditions (age, gender, systolic blood pressure, diastolic blood pressure); underlying diseases (coronary heart disease (CHD), hypertension and diabetes mellitus) were recorded. Fasting venous blood samples (5 ml) were collected under aseptic conditions from the study group after taking informed consent.

Estimation of serum creatinine

The blood samples were collected using BD vacutainer needles into yellow-topped BD gel vacutainers for serum creatinine estimation. The blood samples for serum creatinine were centrifuged at 3000 rpm for 15 min. The serum was separated and stored in storage vials at -70°C until analysis. The method for measurement of serum creatinine is by modification of kinetic Jaffe reaction, and was estimated by using the standard method on the same day of collection by a Roche supplied kit method in Cobas C311 after running quality control samples. This method has a measurement

range of 0.05-20 mg/dl of serum creatinine. The reference range of serum creatinine values was 0.9-1.3 mg/dl in males and 0.6-1.1 mg/dl in females.

Determination of eGFR

The estimated glomerular filtration rate (eGFR) test was applied to assess kidney function and determine the stage of renal disease. The Cockcroft-Gault equation was used to calculate eGFR in both cases and controls: Estimated creatinine clearance (ml/min) = (140-age) body weight (kg)/72Pcr (mg/dl). For women, multiplication is by 0.85. Kidney Disease Outcomes Quality Initiative recommendations [8,9] were employed to determine the CKD stage. In healthy adults, normal eGFR readings are often greater than 60 ml/min/1.73 m^2, at least before the age of 70 years. However, as people become older, their eGFR falls physiologically, and readings below 60 ml/min/1.73 m^2 may be regarded as typical in those over 70 years. Accordingly, stage 1 = GFR 90 ml/min with evidence of kidney damage; stage 2 = GFR 60-89 ml/min with evidence of kidney damage; stage 3 = GFR = 30-59 ml/min – with or without evidence of kidney damage; stage 4 = GFR =15-29 ml/min – with or without evidence of kidney damage, and stage 5 = GFR 15 ml/min – with or without evidence of kidney damage [10].

Estimation of hsCRP by Particle enhanced immunoturbidimetric assay

CRP testing involved using a Cobas C311 (Roche/Hitachi, France). This is an immunoturbidimetric assay for the *in vitro* quantitative detection of CRP in human serum and plasma. It consisted of exposing Human CRP agglutinates to latex particles coated with monoclonal anti-CRP antibodies. Turbidimetric analysis was then employed to determine the aggregates. CRP is a trace protein that can range upwards from 0.8 mg/dL in healthy people. The serum CRP concentration rises swiftly and significantly after the commencement of the acute-phase response. Between 6 to 8 h, changes are visible, and the maximal value is attained within 24 to 48 h. The American Heart Association/Centers for Disease Control Working Group on markers of inflammation in CVD has classified serum hsCRP values of 1, 1-3, and >3 mg/l as low, intermediate, and high-risk groups for global CVD, respectively, based on evidence from population-based studies [10]. The expected value is 0.8 mg/dl.

Estimation of Fibrinogen

A fibroquant kit from Tulip was used to measure fibrinogen levels in blood samples. Fresh citrated plasma coagulates when thrombin reagent is added. The time it takes for blood to clot is proportional to the amount of fibrinogen present. After extracting the needle from the syringe, this allows measurement of plasma fibrinogen using a functional clotting assay. In this research, nine parts of freshly drawn blood were combined with one part sodium citrate (0.11 mol/l, 3.2 percent sodium citrate). The plasma was then transferred to a clean test tube after centrifuging for 15 min at 3000 rpm. Within 3h after collection, plasma was analyzed. In doing so, the plasma samples were diluted (1:8) with Owrens buffer and loaded into separate sample cups with appropriate identity numbers, and the required amount of FIBROQUANT thrombin reagent and washing solution was subsequently added in the respective reagent positions. The fibrinogen concentration in the plasma sample was measured using the FBG programme. The fibrinogen concentration in 1:8 diluted plasmas represents the 100% fibrinogen concentration of the sample. Samples with Fibrinogen mean error (FME) results were retested. The fibrinogen concentration reported by the instrument multiplied by the appropriate dilution factor represents the fibrinogen concentration of the sample.

Estimation of total cholesterol, HDL-cholesterol, triglyceride, LDL, VLDL

A Cobas C311 analyzer was used to measure cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL), and very low density lipoprotein (VLDL). Cholesterol was measured enzymatically with Roche Diagnostics' Cholesterol High-Performance reagent. Triglycerides and cholesterol were tested enzymatically at the same time using reagents as per the manufacturer's instructions. The same reagent was used to measure triglyceride blanks, but without lipase. Roche Diagnostics provides a direct HDL-cholesterol reagent, which was used to measure cholesterol and triglycerides simultaneously. VLDL and LDL determinations were done in the same way. The following are the predicted cholesterol, triglyceride and HDL-cholesterol values: Cholesterol Concentration (mg/dl) – Interpretation: < 200 Desirable, 200-239 Borderline, High > 240, for High Triglyceride Concentration (mg/dl) – Interpretation: < 200 Desirable, 200-400 Borderline, 400-1,000 High and > 1.000 Very High, and for HDL-cholesterol (mg/dl) – Interpretation: < 35 Low, > 60 High. For LDL the values are Optimal – Less than 100 mg/dl, near optimal – 100-129 mg/dl, Borderline high – 130-159 mg/dl, High – 160-189 mg/dl. The VLDL normal levels range from 5-40 mg/dl.

Statistical analysis

Statistica 24.0 was used to perform statistical analysis on the data. The data was given in a tabular format. The study population's demographic features were described via univariate analysis. The significance between the two groups was determined using a student t-test. To see if all of the measures together are significantly superior predictors of cardiovascular events in CKD patients, Chi-square testing was applied. The significant connections between categorical variables were also determined using the Chi-square test. Pearson's correlation was then employed to find a link between all of the different variables. P values of less than 0.05 were deemed significant.

RESULTS

The current study involved 100 CKD stage III and IV patients and 100 control subjects without CKD. All the 100 CKD subjects were non-dialysis patients. Since various biomarkers like serum creatinine, eGFR, hsCRP, fibrinogen, and lipid profile act as early predictors of CAD in CKD at stage III/IV patients, their levels were compared with the control group, i.e. without CKD, in the current study. The CKD III and IV group comprised 60 (60%) males

and 40 (40%) females, whereas the control group contained 68 (68%) males and 32 (32%) females. The mean age group of CKD patients was 54.54 years, and the control group was 54.07 years. Among the 100 subjects in the control and test groups, 38% of the test subjects and 40% of the control subjects were diabetic patients. However, we did not focus on the glycemic status of either the control and test patients. Beyond the aforementioned, 60% of the test patients and 28% of the control patients were hypertensive patients. The results presented in Table 1 and Table 2 show the chi-square test significance of both control and CKD population, respectively. By comparing the serum creatinine levels between the test subjects, i.e. patients diagnosed with CKD, and control subjects, i.e. patients without CKD, the results showed that there was a significant rise in the mean values of serum creatinine for CKD patients (28.76±0.57), compared with control subjects (0.842±0.085). The estimated glomerular filtration rate (eGFR) was decreased significantly for CKD patients (28.37±7.98) when the results were compared with control patients (111.34±14.4). Moreover, the lipid profile mean values (Cholesterol: 214.5±18.8, Triglycerides: 162.1±20.6, VLDL: 32.41±4.13) were high for CKD patients when the results were compared with control patients (Cholesterol: 155.6±16.8, Triglycerides: 129.9.1±12.8, VLDL: 26.04±2.49). In contrast, the mean values of HDL (28.34±4.02 and LDL 153.77±18.2) were less for the CKD group than that for the control group (HDL 40.42±3.99 and LDL 155.64±16.8). There was also a high significant rise in the mean values of hsCRP of CKD patients (34.28±3.257), compared with control patients (7.47±1.488).

In addition, the fibrinogen mean value of the CKD group (291.63±138.7) was comparatively higher than the control group (247.5±48.29).

The results revealed that all the variables were highly significant p <0.00000 and strongly influenced the early detection of cardiovascular events in Chronic Kidney Disease III and IV patients. However, by performing the Pearson's correlation coefficient analysis (Table 3) upon all the study variables, serum creatinine showed significant (p=0.03) negative correlation, and the eGFR demonstrated significant (p=0.01) positive correlation between control and CKD patients, whereas the other variables showed an insignificant positive correlation between control and CKD stage III and IV patients. In this study, higher mean values of hsCRP (34.28 mg/dl), increased serum creatinine levels (2.876 mg/dl), reduced eGFR (28.37 ml/min), high levels of serum fibrinogen (291.6mg/dl) and cholesterol (214.5 mg/dl), HDL (28.34 mg/dl), TG (162.1 mg/dl), VLDL (32.41 mg/dl) and LDL (153.77 mg/dl) are independent predictors of assessment of CV events in patients with CKD stages III and IV as determined by Chi-square test, and play significant roles for the development of CVD in CKD patients stage 3 to 4 (Table 4 and Figure 1).

Figure 1 depicts the higher mean values of hsCRP, increased serum creatinine levels, reduced eGFR, high levels serum fibrinogen and cholesterol. As evident in the figure, HDL, TG, VLDL and LDL are independent predictors of assessment of CV events in patients with CKD stages III and IV.

Table 1. Chi-square test results of control population

Study variables of control population	Mean	Median	Standard deviation	Standard error	95% Confidence level	99% confidence level
Serum Creatinine	0.842	0.8	0.0855	8.55E-03	0.017	0.023
eGFR	111.34	110	14.403	1.4403	2.8579	3.783
Cholesterol	155.61	151	16.8438	1.6844	3.3422	4.424
HDL	40.42	40	3.995	0.4	0.793	1.049
Triglycerides	129.9	128	12.85	1.285	2.55	3.375
VLDL	26.04	25.6	2.4901	0.249	0.4941	0.654
LDL	155.64	151	16.805	1.6805	3.3346	4.414
hsCRP	7.47	7.9	1.4889	0.1489	0.2954	0.391
Fibrinogen	247.57	226	48.2986	4.8299	9.5837	12.68
p<0.000001 (Highly significant)						

Table 2. Chi-square test results of CKD population

Study variables of CKD (test) population	Mean	Median	SDV	SE	95% Confidence level	99% Confidence level
Serum Creatinine	2.876	2.8	0.5702	0.057	0.1131	0.1498
eGFR	28.37	28	7.9819	0.7982	1.5838	2.0965
Cholesterol	214.52	206	18.806	1.8806	3.7316	4.9396
HDL	28.34	28	4.021	0.4020	0.7980	1.0560
Triglycerides	162.1	162	20.66	2.0660	4.1000	5.4270
VLDL	32.41	32.4	4.1322	0.4132	0.8199	1.0854
LDL	153.77	146.4	18.292	1.8292	3.6297	4.8047
hsCRP	34.28	21.5	3.25735	3.2573	6.4634	8.5557
Fibrinogen	291.638	223	138.7385	13.8739	27.5293	36.4409
p<0.0000001 (Highly significant)						

Table 3. Pearson's Correlation between control and CKD subjects

Biomarkers	P (Significance)	R (Correlation)
Serum Creatinine	0.030	-0.217*
eGFR	0.016	0.239*
Cholesterol	0.250	0.116
HDL	0.603	0.053
Triglycerides	0.563	0.059
VLDL	0.510	0.067
LDL	0.222	0.123
hsCRP	0.141	0.148
Fibrinogen	0.425	0.081

Table 4. Comparison of parameters between CKD and Control groups

Parameters	CKD group Mean ±SD/median	Control group Mean ±SD/median	P value
Serum Creatinine	2.876±0.5702	0.842±0.0855	<0.000001*
eGFR	28.37±7.9819	111.34±14.403	<0.00001*
Cholesterol	214.52±18.806	155.61±16.8438	<0.0001*
HDL	28.34±4.021	40.42±3.995	<0.000001*
Triglycerides	162.1±20.66	129.9±12.85	<0.00001*
VLDL	32.41±4.1322	26.04±2.4901	<0.000001*
LDL	153.77±18.292	155.64±16.805	<0.0001*
hsCRP	34.28±3.25735	7.47±1.4889	<0.000001*
Fibrinogen	291.638±138.7385	247.57±48.2986	<0.00001*

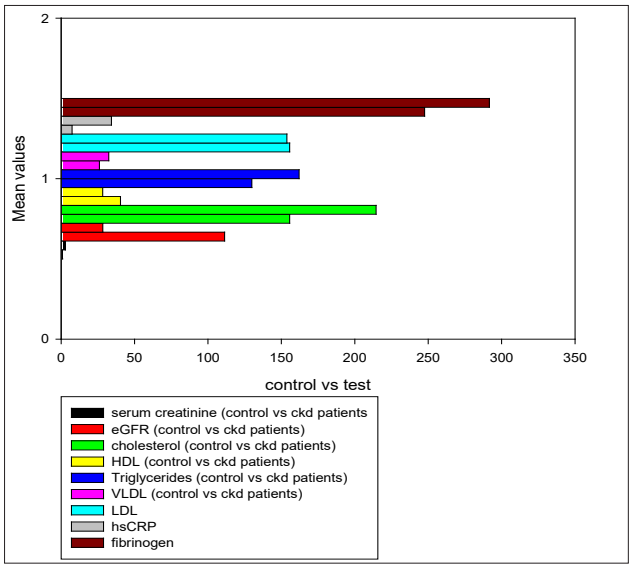

Figure 1. The biomarker mean values for control and CKD patients

DISCUSSION

The kidneys and heart are closely related with regard to heart failure, and CKD patients have a high risk of CVD, according to numerous studies. Despite dialysis, the annual mortality rate in India for ESRD is above 20%, with cardiovascular disease accounting for more than half of the deaths. People with end-stage CKD (dialysis) have a five-fold lower life expectancy from cardiovascular disease as compared to healthy people.

In 1998, the National Kidney Foundation's Task Force on CVD in CKD issued research underlining the increased risk of CVD in people with CKD [11]. These findings revealed a high frequency of CVD in people with CKD and the fact that CVD-related mortality in dialysis patients was 10 to 30 times greater than in the general population. A variety of cardiovascular biomarkers have recently been identified as predictors of patient outcome in persons with CVD. With additional research, they may be exploited to guide early CVD diagnosis and therapy in persons with CKD [12-14].

In our study, according to the chi-square test and Pearson's correlation analysis, elevated levels of hsCRP, serum creatinine, decreased eGFR, serum fibrinogen and dyslipidemia are independent predictors of evaluation of CV events in patients with CKD stages 3 and 4. These biomarkers have been found to play a key role in the course of CVD in patients with chronic kidney disease. Factors including demographics, cardiovascular illness and kidney disease have no bearing on this collaboration. A decline in kidney function has constantly been shown to be an independent risk factor for cardiovascular disease and all-cause mortality in patients following heart attacks, those undergoing coronary procedures, patients with heart failure, and patients with hypertension or diabetes and elderly subjects. However, this association has been inconsistent in prospective investigations of broad populations. The majority of the CKD patients in this study were under the age of 54. The most prevalent aetiologies of CKD were diabetes mellitus, chronic glomerulonephritis, and hypertension (among others), which was consistent with earlier data [15-22].

In individuals with CKD, highly selective C-reactive protein has been quite effective in determining cardiovascular risk. Control patients with mean hsCRP values of 7.47 mg/dl had no chance of CVD risk, whereas CKD participants with serum hsCRP levels of 34.28mg/dl had a moderate to high cardiovascular incident risk [21-24]. This study found that CKD patients in stages 3 and 4 have a significantly greater risk of cardiovascular events. The median serum level of hsCRP in the CKD population was considerably more significant than in the controls (who did not have CKD). This study reveals that the inflammatory process in CKD begins before dialysis and is not solely due to dialysis, as the CKD patients in this study were dialysis naive. Inflammation, as measured by CRP level, increases with decreasing renal function in CKD patients in stages 3 to 4, according to this study.

Renal dysfunction in heart failure patients can be complicated and multifaceted, with decreased renal perfusion and venous blockage being the most common causes [25,26]. Inflammatory and cellular immune-mediated mechanisms; stress-mediated and neurohormonal responses; metabolic and nutritional changes, such as bone and mineral disorders, altered haemodynamic and acid-base or fluid status, anaemia growth and intrinsic tubular harm are among the other mechanisms involved in the process.

Many variables, including dyslipidemia, can cause renal impairment in heart failure patients [27]. Dyslipidemia is a well-known cardiovascular (CV) risk factor in the general population. However, epidemiologic studies and clinical trials in CKD [27-30] have cast doubt on the impact of dyslipidemia on clinical outcomes and, as a result, the optimum lipid profile. In the general population, high LDL cholesterol, low HDL cholesterol, and, to a lesser extent, high total triglyceride levels are all connected to higher atherosclerotic CV risk [31]. The bulk of the research in dialysis populations, including cross-sectional and longitudinal studies, does not indicate a clear link between dyslipidemia and CVD [30-32]. This ostensibly atypical relationship may be attributed, in part, to the methods used to measure dyslipidemia. However, the results in the current study were varied compared to earlier studies wherein high plasma cholesterol (214.5 mg/dl), low concentration of HDL (28.34 mg/dl) and higher concentration of TGs (162.1 mg/dl), VLDL (32.41 mg/dl) and LDL (153.77) were more commonly reported in CKD patients, as compared to control subjects. Furthermore, as indicated by Attman and Alaupovic [32], the atherogenic potential of dyslipidemia in CKD can rely more on the apolipoprotein than on lipid abnormalities and may not always be recognized by measuring plasma lipids alone.

The present study reported lower GRF and high serum creatinine concentration (2.876 mg/dl) in CKD patients (28.37 mL/min·1.73 m^2). Shlipak *et al.* [33] reported that 11% of all participants had an eGFR < 60 mL/min·1.73 m^2, indicating that CKD is highly prevalent in patients with CAD patients, especially heart failure patients. The results were consistent with the present study. Similarly, Garg *et al.* [34] and Muntner *et al.* [2] showed similar findings and were consistent with the present study.

In this investigation, a plasma fibrinogen level of 291.638 mg/dl was shown to be substantially linked to a higher risk

of CVD. In our study, high plasma fibrinogen levels demonstrated a considerable linkage with CV and all-cause mortality, which is similar to findings from several investigations on patients with stage 3-4 CKD [35-37]. In the literature, researchers put forth that nonenzymatic glycosylation and fibrinogen oxidation have impact upon the characteristics of clots in CKD patients. Nonenzymatic glycosylation and oxidized fibrinogen can reduce clot permeability, increase fiber density, or decrease porosity in combination with a smaller individual fiber diameter, resulting in a higher proportion of thin fibers and the formation of stiffer clots that are less sensitive to plasmin and more difficult to lyse. Increased clot density owing to high fibrinogen levels in dialysis patients has been associated with CV and all-cause mortality separately and strongly [38-40].

CONCLUSION

In this paper, the authors analyzed the use of established and significant laboratory biomarkers for assessing CKD risk in the general population. The high rate of CVD events and premature mortality in patients with CKD, a sharp rise in risk as GFR falls below 60 mL/min/1.72 m^2, higher serum creatinine, C-reactive protein, dyslipidemia, fibrinogen, and other factors, provide a foundation for improved risk stratification in the general population. The increased rate of CV problems found in CKD patients is attributable to a mix of traditional risk factors, as well as those that are more intimately tied to the loss of renal function (anemia, oxidative stress, inflammation, and bone mineral disorders). This technique implies that a prompt and accurate assessment of cardiovascular risk will enable more aggressive and focused treatment of individuals who are most in need of preventive interventions to decrease incident rates.

ACKNOWLEDGMENT

The authors thank the authorities of GIMSR, GITAM (Deemed to be University), Visakhapatnam and Tertiary Care Teaching Hospital, Visakhapatnam for providing infrastructural facilities.

FUNDING AGENCY

No funding and grants to support this work.

CONFLICT OF INTEREST

The authors declared, "No conflict of interest."

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REFERENCES

1. Abraham G, Moorthy AV, Aggarwal V. Chronic Kidney Disease: a silent epidemic in Indian subcontinent-strategies for management. *J Ind Med Assoc*. 2006;104(12):689-91.
2. Muntner P, Jiang He, Hamm L, Loria C, Whelton PK. Renal insufficiency and subsequent death from cardiovascular disease. *J Am Soc Nephrolgy*. 2002;13:745-53.
3. Kuhn A, van der Giet M, Kuhlmann MK, Mielke N, Ebert N, Schaeffner ES, et al. Kidney function as risk factor and predictor of cardiovascular outcomes and mortality among older adults. *Am J Kidney Dis*. 2021;77(3):386-96.
4. Fu EL, Franko MA, Obergfell A, Dekker FW, Gabrielsen A, Jernberg T, Carrero JJ. High-sensitivity C-reactive protein and the risk of chronic kidney disease progression or acute kidney injury in post-myocardial infarction patients. *Am Heart J*. 2019;216:20-9.
5. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351(13):1296-305.
6. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39(2 Suppl 1):S1-266.
7. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. K/DOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis*. 2014;63(5):713-35.
8. Roberts WL. CDC/AHA workshop on markers of inflammation and cardiovascular disease: Application to Clinical and Public Health Practice: laboratory tests available to assess inflammation – performance and standardization: a background paper. *Circulation*. 2004;110(25):572-6.
9. Fraser SD, Roderick PJ, Aitken G, Roth M, Mindell JS, Moon G, et al. Chronic kidney disease, albuminuria and socioeconomic status in the Health Surveys for England 2009 and 2010. *J Public Health* (Oxf.) 2014;36(4):577-86.
10. Tonelli M, Wiebe N, Guthrie B, James MT, Quan H, Fortin M, et al. Comorbidity as a driver of adverse outcomes in people with chronic kidney disease. *Kidney Int*. 2015;88(4):859-66.
11. Jankowski J, Floege J, Fliser D, Bohm M, Marx N. Cardiovascular disease in chronic Kidney Disease. *Circulation*. 2021;143(11):1157-72.
12. Balagopal PB, De Ferranti SD, Cook S, Daniels SR, Gidding SS, Hayman LL, et al. Nontraditional risk factors and biomarkers for cardiovascular disease: mechanistic, research, and clinical considerations for youth: a scientific statement from the American Heart Association. *Circulation*. 2011;123:2749-69.
13. Atkinson AJ, Colburn WA, DeGruttola VG, DeMets DL, Downing GJ, Hoth DF, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001; 69:89-95.
14. Manolio T. Novel risk markers and clinical practice. *N Engl J Med*. 2003;349:1587-9.
15. Bash LD, Erlinger TP, Coresh J, Marsh-Manzi J, Folsom AR, Astor BC. Inflammation, hemostasis, and the risk of kidney function decline in the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis*. 2009;53:596-605.
16. Erlinger TP, Tarver-Carr ME, Powe NR, Appel LJ, Coresh J, Eberhardt MS. Leukocytosis, hypoalbuminemia, and the risk for chronic kidney disease in US adults. *Am J Kidney Dis*. 2003; 42:256-63.
17. Fried L, Solomon C, Shlipak M, Seliger S, Stehman-Breen C, Bleyer AJ, et al. Inflammatory and prothrombotic markers and the progression of renal disease in elderly individuals. *J Am Soc Nephrol*. 2004;15:3184-91.
18. Langston RD, Presley R, Flanders WD, McClellan WM. Renal insufficiency and anaemia are independent risk factors for death among patients with acute myocardial infarction. *Kidney Int*. 2003;64:1398-405.
19. Keeley EC, Kadakia R, Soman S, Borzak S, McCullough PA. Analysis of long-term survival after revascularization in patients with chronic kidney disease presenting with acute coronary syndromes. *Am J Cardiol*. 2003;92:509-14.
20. Matthew J. Tunbridge, Alan G. Jardine. Atherosclerotic Vascular Disease associated with chronic kidney disease. *Cardiology Clinics*. 2021;39(3):403-14.
21. Hak AE, Stehouwer CD, Bots ML, Polderman KH, Schalkwijk CG, Westenorp IC, et al. Associations of C-reactive protein with measures of obesity, insulin resistance, and subclinical atherosclerosis in healthy, middle-aged women. *Arterioscler Thromb Vasc Biol*. 1999; 19:1986-91.
22. Elkind MS, Tai W, Coates K, Paik MC, Sacco RL. High-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2, and outcome after ischemic stroke. *Arch Intern Med*. 2006;166: 2073-80.

23. Arici M, Walls J. End stage renal disease, atherosclerosis, and cardiovascular mortality: Is C-reactive protein the missing link? *Kidney Int*. 2001;59:407-17.
24. Menon V, Greene T, Wang X, Pereira AA, Marcovina SC, Beck GJ, et al. C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. *Kidney Int*. 2005; 68:766-72.
25. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol*. 2009;53:589-96.
26. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2000;35:681-9.
27. Iseki K, Yamazato M, Tozawa M, Takishita S. Hypocholesterolemiais a significant predictor of death in a cohort of chronic hemodialysis patients. *Kidney Int*. 2002;61:1887-93.
28. Kaysen GA. New insights into lipid metabolism in chronic kidney disease. *J Ren Nutr*. 2011;21:120-3.
29. Goldstein JL, Kita T, Brown MS. Defective lipoprotein receptors and atherosclerosis. *N Engl J Med*. 1983;309:288-96.
30. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. *Am J Med*. 1977;62:707-14.
31. Rifkind BM, Segal P. Lipid Research Clinics Program reference values for hyperlipidemia and hypolipidemia. *JAMA*. 1983;250:1869-72.
32. Attman PO, Alaupovic P. Lipid and apolipoprotein profiles of uremic dyslipoproteinemia: Relation to renal function and dialysis. *Nephron*. 1991;57:401-10.
33. Shlipak MG, Simon JA, Grady D, Lin F, Wenger NK, Furberg CD. Renal insufficiency and cardiovascular events in postmenopausal women with coronary heart disease. *J Am Coll Cardiol*. 2001;38: 705-11.
34. Modi ZJ, Lu Y, Ji N, et al. Risk of Cardiovascular Disease and Mortality in Young Adults With End-stage Renal Disease: An Analysis of the US Renal Data System. *JAMA Cardiol*. 2019;4(4): 353-62.
35. Zoccali C, Mallamaci F, Tripepi G, Kapke A, Selewski DT, Dietrich X, et al. Fibrinogen, mortality and incident cardiovascular complications in endstagerenal failure. *J Intern Med*. 2003;254(2): 132-9.
36. Undas A, Nycz K, Pastuszczak M, Stompor T, Zmudka K. The effect of chronic kidney disease on fibrin clot properties in patients with acute coronary syndrome. *Blood Coagul Fibrinolysis*. 2010;21(6):522-7.
37. Collet JP, Allali Y, Lesty C, Tanguy ML, Silvain J, Ankri A, et al. Altered fibrin architecture is associated with hypofibrinolysis and premature coronary atherothrombosis. *Arterioscler Thromb Vasc Biol*. 2006;26(11):2567-73.
38. Kearney K, Tomlinson D, Smith K, Ajjan R. Hypofibrinolysis in diabetes: a therapeutic target for the reduction of cardiovascular risk. *Cardiovasc Diabetol*. 2017;16:34.
39. Parastatidis I, Thomson L, Burke A, Chenysh J, Nagaswami C, Visser J, et al. Fibrinogen beta-chain tyrosine nitration is a prothrombotic risk factor. *J Biol Chem*. 2008;283(49):33846-53.
40. Lee SJ, Hong JM, Lee, SE, Kang DR, Ovbiagele B, Dermchuk AM, et al. Association of fibrinogen level with early neurological deterioration among acute ischemic stroke patients with diabetes. *BMC Neurol*. 2017;17:101.