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Lipoprotein (a) Cut-Off in Chronic Kidney Disease Patients with a History of Cardiovascular Disease in Center Hospital University Souro SANOU, Burkina Faso

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Abstract

Patients living with chronic kidney disease (CKD) are at high risk of cardiovascular events. Our aim in this study was to assess the cut-off value for lipoprotein (a) (Lp(a)) in CKD patients with a history of cardiovascular disease (CVD). This was a cross-sectional study. Variables including age, sex, history of CVD, body mass index and CKD stage, were collected during CKD patient's first admission in the nephrology dialysis department. Blood samples were collected for quantitative determination of Lp(a) by immunoturbidimetric method. They were divided into two groups: CKD patients without history of CVD and CKD patients with history of CVD. Fisher's exact test was used to assess associations with a significance level of 0.05%. Area under the curve (AUC) and new cut-off value for Lp(a) were identified by drawing Receiver Operating Characteristic (ROC) curve. A total of seventy CKD patients with median age of 43 years [minimum-maximum = 15 - 78 years] were included. Patients with history of CVD were 65.71% (46/70). New Lp(a) cut-off point in CKD patients with history of CVD was 66.50 nmol/L [sensitivity, 87.00%; specificity, 58.30%; AUC = 0.727; p = 0.000]. ROC curve demonstrated good performance of Lp(a) to screen CKD patients with history of

CVD. Further research is needed to determine an LPA gene polymorphism's contribution to increasing risk for CVD at each kidney disease stage.

Keywords

Lipoprotein (a), Cut-Off, Chronic Kidney Disease, Cardiovascular Disease

1. Introduction

Chronic kidney disease results in disturbances of lipid metabolism, including elevated Lp(a), a common independent atherosclerotic CVD risk factor [1]. CVD is the main cause of morbidity and mortality in patients at every stage of CKD [2] [3]. CVD occurs early in CKD patients and many patients have CVD during their nephrology following [4]. Systematic reviews show that elevated Lp(a) concentration values were associated with a higher risk of fatal and non-fatal cardiovascular events in patients with CKD [5]. Lp(a) concentration is mainly genetically regulated by the LPA gene, coding for apolipoprotein (a) [apo (a)] [6], but the genetic variants significantly involved in cardiovascular disease have not been fully elucidated [7]. Lp(a) concentration is not routinely determined in patients admitted to the nephrology-dialysis department. Moreover, several practical cut-offs for Lp(a), over 75 nmol/L for the risk of CVD, have been proposed [8]. The present study was conducted to assess the cut-off value for Lp(a) in CKD patients with a history of cardiovascular disease (CVD) during their first admission to the nephrology-dialysis department.

2. Methodology

2.1. Study Population and Sampling

This was a cross-sectional study conducted over three months, from September to November 2019. CKD patients admitted for the first time in the nephrology-dialysis department and consent to participate in our study were included. Non-consenting patients, dialysis patients, and patients with acute renal failure were excluded. They were then divided into two groups: CKD patients without history of CVD and CKD patients with a history of CVD.

2.2. Data Collection and Variables

Demographic and clinical variables collected were age, gender, and body mass index (BMI). Biochemical variables collected were serum Lp(a) and creatinine.

2.3. Blood Samples and Biochemical Parameters

Blood samples and biochemical parameters

Blood samples were taken from fasting patients in dry tubes by venipuncture. The serum was collected after centrifugation at 4000 rpm for 3 minutes. Aliquots of 1.5 millilitres were kept at −20˚C.

Biochemical parameters were measured on Roche systems Cobas® 6000 (France, Roche/Hitachi). Creatininemia was determined by modifying Jaffe's kinetic method. Lp(a) concentration was determined by particle-enhanced turbidimetric immunoassay with Tina-quant Lipoprotein (a) Gen.2 (LPA2) (Roche Diagnostics GmbH, Germany).

2.4. Data Analysis

Data were analyzed on XLSTAT 2019.4.2 for mean ± standard deviation, median, minimum and maximum values and Fisher's exact test was used to assess associations with a significance level of 0.05%. The glomerular filtration rate was estimated by the Modification of Diet in Renal Disease (MDRD) formula [9]. With the area under the ROC curve analysis, a new Cut-off value was calculated for Lp(a) in CKD patients with history of CVD.

2.5. Ethical Considerations

Informed consent was obtained from all chronic kidney disease patients with or without CVD history in this study. They were alerted about the high morbidity and mortality rate observed in patients with both CKD and cardiovascular disease. Their participation was completely voluntary. Biological samples were well labeled and all data were processed in anonymity.

3. Results

3.1. General Characteristics of the Study Population

The study included 70 patients with chronic kidney disease. The gender distribution was 60.00% (42/70) of males with a sex ratio (M/F) of 1.50. Their median age was 43 years [minimum-maximum = 15 - 78 years]. CKD patients with history of CVD were 65.71% (46/70) and were not associated significantly with sex ($p = 0.959$), age group ($p = 0.570$), BMI ($p = 0.686$), GFR ($p = 0.316$) (**Table 1**).

3.2. ROC Curve for CKD Patients with History of CVD

Lipoproteinemia (a) median value in CKD patients with history of CVD was 130.50 nmol/L (minimum-maximum = 14.50 - 351 nmol/L) and was not significantly different from CKD patients without history of CVD ($p = 0.097$) (**Table 2**).

Lp(a) cut-off point in CKD patients with history of CVD was 66.50 nmol/L. AUC obtained is 0.727 (95% CI = 0.600 - 0.855) (**Figure 1**).

The sensitivity, specificity, predictive positive value (PPV) and predictive negative value (PNV) were 87.00% (95% CI = 73.7 - 95.10), 58.30% (95% CI = 36.60 - 77.90), 80.00% and 70.00% respectively.

4. Discussion

The median Lp(a) level was not significantly higher in CKD patients with history of CVD. Lp(a) levels remain unaffected by most clinical conditions, due to the strong genetic control of the LPA gene coding for apolipoprotein (a). However,

high concentrations of Lp(a) have been reported in patients with nephrotic syndrome, end-stage renal disease or during dialysis treatment [10]. Lifelong exposure to higher concentrations of Lp(a) is associated with an increased risk of

Table 1. Characteristics of patients with history of CVD.

Patients characteristics	Study population (n = 70)	History of CVD:		p-value
		Yes (n = 46)	No (n = 24)	
Sex				0.959
F	28 (40.00)	18 (25.71)	10 (14.29)	
M	42 (60.00)	28 (40.00)	14 (20.00)	
Age (years)				0.570
[15 - 30[	12 (17.14)	7 (10.00)	5 (7.14)	
[30 - 45[	27 (38.57)	19 (27.14)	8 (11.43)	
[45 - 60[	18 (25.71)	11 (15.71)	7 (10.00)	
[60 - 75[	12 (17.14)	9 (12.86)	3 (4.29)	
>75	1 (1.43)	0 (0.00)	1 (1.43)	
BMI (kg/m^2)				0.686
<18.5	19 (27.14)	11 (15.71)	8 (11.43)	
[18.5 - 24.9]	40 (57.14)	27 (38.57)	13 (18.57)	
[25.0 - 29.9]	6 (8.57)	5 (7.14)	1 (1.43)	
>30	5 (7.14)	3 (4.29)	2 (2.86)	
GFR (mL/min/1.73m^2)				0.316
[15 - 29]	12 (17.14))	6 (8.57)	6 (8.57)	
[0 - 15[	58 (82.86)	40 (57.14)	18 (25.71)	

CVD = Cardiovascular disease; BMI = Body mass index; GFR = Glomerular Filtration Rate.

Table 2. Lp(a) concentration in patients with history of CVD.

Biochemical parameters	Study population (n = 70)	History of CVD:		p-value
		Yes (n = 46)	No (n = 24)	
Lp(a) (nmol/L)				
Median (min-max)	124.20 (2.40 - 351.80)	130.50 (14.50 - 351.80).	62.40 (2.40 - 333.40)	0.097
Mean ± SD	146.59 ± 106.16	172.46 ± 105.48	97.00 ± 90.21	
Creatinemia (µmol/L)				
Median (min-max).	1147.30 (221.00 - 4463.40)	1251.45 (221.00 - 4246.34).	864.05 (241.60 - 4463.40)	0.244
Mean ± SD	1350.35 ± 970.77	1416.37 ± 888.10	1223.84 ± 1121.89	

CVD = Cardiovascular disease; SD = Standard deviation.

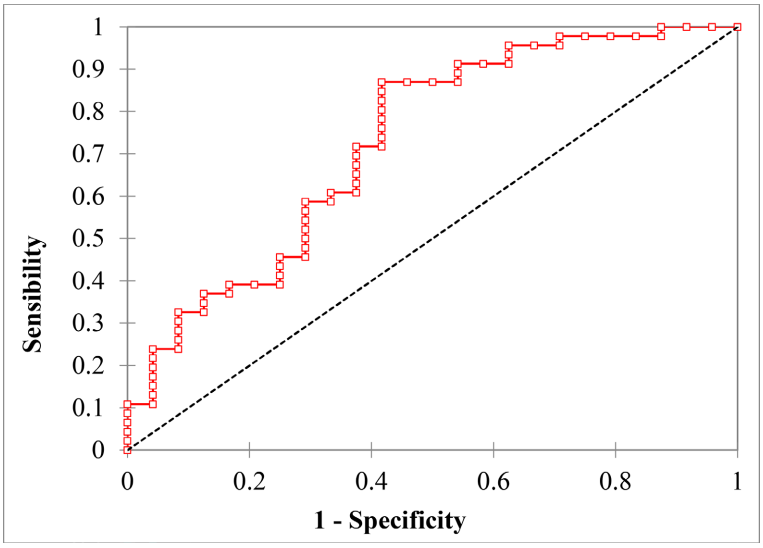

Figure 1. ROC curve for CKD patients with history of CVD using the Lp(a).

CVD [11]. Generally, cardiovascular disease is the main cause of morbidity and mortality in patients with CKD, who are more likely to die from CVD before reaching end-stage renal disease [4]. A large number of studies have investigated Lp(a) in end-stage renal disease patients [12] [13], and elevated Lp(a) levels have been observed in patients undergoing hemodialysis or peritoneal dialysis [12].

The cut-off value for Lp(a) in the detection of CKD patients with a history of CVD, was found to be 66.50 nmol/L. This calculated cut-off value was lower than the standard cut-off value of 75 nmol/L which was arbitrarily selected as the clinical decision in the white population [8].

There are many challenges to determining a common Lp(a) cut-off level in laboratories, including differences in measurement units and techniques, heterogeneity in values reported in different studies, pronounced variations in Lp(a) concentrations between different racial groups [14] and in individuals with co-morbidities (such as chronic renal failure, liver disease and hypothyroidism [15].

Many studies on Lp(a) have been performed in white populations, limiting applicability to other ethnic or racial groups [16]. Consequently, the standard cut-off value of 75 nmol/L cannot be applied to our population. Specific cut-off values are needed in clinical practice to identify individuals at risk of CVD requiring intervention [16]. The 2010 European Atherosclerosis Society Consensus Panel recommended using an Lp(a) cutoff value of 50 mg/dl (≈120 nmol/L) [17]. The patient should be from the same race/ethnicity as the one used to establish the cut point. For patients who are black, Japanese, or from other ethnic/racial groups, no such cut points have been established [16]. A study in four ethnic groups demonstrated a similar ethnic-specific difference: mean Lp[a] concentrations in Ghanaians was 77.28 ± 75.60 nmol/L and was 1.6 to 2-fold higher than those of German, Chinese, or San populations, respectively [18]. Recent studies in a multi-ethnic population have emphasized the importance of race/ethnicity

as a key variable in assigning Lp(a) cut-off values for CVD risk assessment and the need to develop the most clinically useful Lp(a) cutoff values in individual race/ethnicity groups [19]. This Area under the ROC curve (AUC) of 0.727 indicates a significant diagnostic value for Lp(a) in the detection CKD patients with a history of CVD [20].

5. Conclusion

This preliminary study suggests that 66.50 nmol/L is a practical lipoprotein (a) cut-off for the history of CVD in chronic kidney disease patients and also the need for systematic screening of Lp(a) levels in patients with CKD, due to the high morbidity and mortality rate observed in patients with both CKD and cardiovascular disease. Further studies are needed to determine whether elevated Lp(a) or LPA gene polymorphisms contribute to the increased risk of cardiovascular disease at each stage of kidney disease.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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