

Original Article

## Factors Affecting the Development of Cardiovascular Events Among Patients with End-Stage Renal Disease Undergoing Hemodialysis in Sudan

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**Received:** 13.06.2017; **Accepted:** 14.07.2017

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**Cite this article as:** Amir O, Sarriff A, Abdelraheem MB, Khan AH, Norsa'adah B. Factors Affecting the Development of Cardiovascular Events among Patients with End-Stage Renal Disease Undergoing Hemodialysis in Sudan. J Basic Clin Health Sci 2017; 3: 61-5.

### Abstract

**Purpose:** This study aimed to determine factors that affected the development of new onset cardiovascular events among patients with end-stage renal disease (ESRD) undergoing hemodialysis (HD) at the Khartoum HD centers in Sudan.

**Methods:** A prospective observational study was conducted among anemic ESRD patients undergoing HD at Khartoum State HD centers. A total of 1015 patients undergoing HD were recruited from 12 HD centers. A standardized data collection form was used for collecting the required data. Logistic regression analysis was performed.

**Results:** Of 1015 recruited patients, 534 (52.6%) were included in the final analysis; the 481 patients who were excluded comprised 194 (19.1%) patients who were transferred to other centers, 165 (16.3%) who died, 84 (8.3%) who were lost during follow-up, and 38 (3.7%) who underwent renal transplantation. The significant factors that affected the development of new cardiovascular events in 154 (28.8%) anemic ESRD patients were advanced age [for patients aged 45-64 years: odds ratio (OR), 1.94; 95% confidence interval (CI), 1.18-3.18;  $p=0.009$  and for patients aged  $\geq 65$  years: OR, 10.88; 95% CI, 6.12-19.33;  $p<0.001$ ] and obstructive uropathy (OR, 2.33; 95%, 1.34-4.03;  $p=0.003$ ).

**Conclusion:** Advanced age and obstructive uropathy were important factors that significantly affected the development of cardiovascular events in patients. The detection and control of risk factors for cardiovascular events in patients with ESRD are important for the prevention or control of cardiovascular events.

**Keywords:** End-stage renal disease, anemia, hemodialysis, cardiovascular events, risk factors, Sudan

### INTRODUCTION

End-stage renal disease (ESRD) is a major public healthcare problem, particularly in developing countries. Cardiovascular problems were commonly found in patients with ESRD as consequences and complications of anemia, which manifested as fatigue, reduced exercise capacity, decreased cognition, and impaired immunity; these eventually led to a decreased quality of life (1). There are strong associations between anemia and cardiovascular complications, as well as morbidity, mortality and patient quality of life (2-4). The traditional or coronary risk factors for cardiovascular disease (CVD) were derived from the Framingham studies (5, 6). The most important factors were arterial hypertension (HTN), diabetes mellitus (DM), advanced age, male sex, family history, menopause, dyslipidemia, low high-density lipoprotein levels, obesity, and low physical activity (7-10). The INTERHEART Africa and sub-Saharan Africa studies documented that HTN was the most common CVD risk factor in black Africans (11,12). However, DM, smoking, dyslipidemia, and abdominal obesity were important risk factors for ischemic heart disease (IHD) in sub-Saharan Africa (12). Nontraditional or uremia-related factors have a role in enhancing IHD and were elevated with the prevalence and severity of CVD and chronic kidney disease (CKD) (7). Kendrick and Chonchol (13) reported that microalbuminuria, low hemoglobin (Hb) levels, oxidative stress, high inflammation, and bone and mineral metabolism abnormalities were major nontraditional cardiac risk factors in patients undergoing HD. Despite the high prevalence of CVD among patients undergoing HD, the factors that affected the development of CVD were unknown in Sudan. Therefore, this study was conducted to identify factors that enhanced the development

of cardiovascular events among patients with anemic ESRD undergoing HD at Khartoum HD centers.

## METHODS

A prospective observational longitudinal study was conducted in governmental HD centers in Khartoum from August 1, 2012 to July 31, 2013. Khartoum is the capital of Sudan, which is situated in the Central Africa. Khartoum covers an area of 22,736 km<sup>2</sup>, with a total population of 7,152,102, mainly comprising Sudanese. A sample size of 1015 patients was calculated using the power and sample size (PS) software (14, 15). Of 24 HD centers distributed across Khartoum, 12 were stratified, and adult (aged ≥18 years) patients with confirmed ESRD undergoing HD for ≥4 months were recruited. Before data collection, all patients were informed about the aim of the study; those who signed an informed consent were identified and followed-up until they were transferred to other centers, underwent renal transplantation, lost to follow-up, continue to the end of the study, or died. An equal number of patients Eighty-five patients who fulfilled the inclusion criteria were recruited from each center, and they were selected using non-probability convenient sampling. Patients with other chronic diseases such as malignancy and rheumatoid arthritis were excluded.

A standardized data collection form was used to collect data regarding patients' sociodemographic characteristics data such as age, sex, race, height, and dry weight (i.e., the weight of the patient at the time of recruitment, necessary to perform well-tolerated dialysis sessions without hypotension); social factors such as insurance status, education level, employment status, monthly income, and marital status; social habits such as smoking and alcohol consumption; and medical records that were reviewed for clinical factors such as comorbidities, ESRD etiology and its duration, and laboratory data. The Modification of Diet in Renal Diseases equation, namely glomerular filtration rate (GFR) (ml/min/1.73 m<sup>2</sup>) =  $186 \times (S_{cr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American})$ , was used for estimating GFR based on the study by Levey et al. (16). The body mass index of patients was calculated as weight in kilograms divided by height in meters squared and was categorized into five standard groups according to the World Health Organization (17). The complete blood count test was performed to determine Hb levels and other anemia parameters. According to the 2012 Kidney Disease Improving Global Outcomes Anemia Work Group, the definition of anemia was an Hb level of <13.0 g/dL (<130 g/L) in males and <12.0 g/dL (<120 g/L) in females (18). New cardiovascular events, confirmed based on cardiology investigations, were noted and recorded from the patients' medical records and during the patients' direct interview, which was performed during the monthly follow-up. Other data recorded were laboratory test results, medications used, and clinical outcomes, as determined by hospitalization and mortality rates.

This study was approved by the National Center for Kidney Diseases and Surgery, Ministry of Health, Republic of Sudan, and other approvals from centers were obtained for the selection of patients.

## Statistical Analysis

Statistical Package for Social Sciences software version 22.0.1 (IBM Corp.; Armonk, NY, USA) was used for data analysis,

and variables with p values of <0.05 were considered to be statistically significant. Continuous variables were expressed as mean and standard deviation, and categorical variables were stated as frequency and percentages. Logistic regression analysis was performed, and an odds ratio (OR) of >1 was considered to be a significant factor. The association between cardiovascular events (no/yes) (dichotomous dependent variable), and patients' sociodemographic and clinical characteristics as independent variables, was assessed. The two categorical independent variables were used as dichotomous (no/yes) and more than two categorical variables introduced into the logistic regression models as dummy variables using the procedures according to Field A (19). In univariate analysis, sociodemographic and clinical-independent variables were individually introduced in the model with cardiovascular events (no/yes), and binary logistic regression was performed. The factor that were considered to be a predictor that affected the development of cardiovascular events was judged to be significant at p values of <0.05 [95% confidence interval (CI)] and an unadjusted OR of >1.

Subsequently, for multivariate analysis, the patients' sociodemographic and clinical variables were introduced into one model with cardiovascular events (no/yes) as dependent variable. The backward stepwise method was used. Finally, in the final model, all significant variables (p<0.025) in the previous multivariate model were introduced using the backward stepwise method. The adjusted OR >1 at a significance level <0.05 (95% CI) of was expressed as significant factor.

## RESULTS

Of 1015 patients recruited for the study, 194 (19.1%) were transferred to other centers, 165 (16.3%) were announced dead, 84 (8.3%) were lost to follow-up, and 38 (3.7%) underwent renal transplantation. Finally, 534 (52.6%) patients were included. The majority of patients (307; 57.5%) were males. The overall mean age of the patients was 48.66±16.05 years. The frequencies of the patients' baseline socio-demographic characteristics and clinical factors are shown in Tables 1 and 2, respectively. During follow-up, 154 (28.8%) patients experienced cardiovascular events, such as left ventricular hypertrophy (8; 52.6%), IHDs (26; 16.8%), heart failure (17; 11%), stroke (16; 10.4%), transient ischemic attack (eight; 5.2%), and peripheral vascular diseases (six; 3.9%).

The significant factors with unadjusted ORs are presented in Table 3. However, the significant factors in the multivariate model were advanced age (≥65 years), HTN, obstructive uropathy, and other comorbid diseases (i.e., diseases other than the stated one and not commonly found among the study subjects) (Table 3). Table 4 illustrates the factors substantially affected the development of cardiovascular events among study patients. Those were advanced age of 45-64 years and age of ≥65 years. Those were twice times and 11 times the odds to affecting the development of cardiovascular events more than younger patients. In addition, patients with obstructive uropathy as the leading cause of ESRD were twice times more likely to experience the development of cardiovascular events (p=0.003) than those without obstructive uropathy undergoing HD.

**Table 1.** Sociodemographic characteristics of 534 patients with anemic ESRD undergoing hemodialysis

Variable	n (%)
<b>Sex</b>	
Male	307 (57.5)
Female	227 (42.5)
<b>Age (years)</b>	
18-44	198 (37.1)
45-64	234 (43.8)
≥65	102 (19.1)
<b>BMI (kg/m<sup>2</sup>)</b>	
Underweight (<18.5)	129 (24.2)
Normal weight (18.5-24.9)	390 (73.0)
Overweight (≥25)	15 (2.8)
<b>Race</b>	
Sudanese	528 (98.9)
Others	6 (1.1)
<b>Insurance status</b>	
Uninsured	232 (43.4)
Insured	302 (56.6)
<b>Education level</b>	
≥Secondary	349 (65.4)
<Secondary	185 (34.6)
<b>Employment status</b>	
Unemployed	301 (56.4)
Employed	233 (43.6)
<b>Monthly income (SDG)</b>	
<1000,000	431 (80.7)
≥1000,000	103 (19.3)
<b>Smoking habit</b>	
Current	3 (0.6)
Previous	244 (46.3)
Never	287 (53.7)
<b>Alcohol intake</b>	
Previous	104 (19.5)
Never	430 (80.5)
<b>Family history of ESRD</b>	
No	450 (84.3)
Yes	84 (15.7)

BMI: Body Mass Index; SDG: Sudanese Pound; ESRD: end-stage renal disease

## DISCUSSION

It was observed that 29% of the patients experienced cardiovascular events, which was higher than the 20.8% observed in the Chinese study by Tong et al. (20). However, the U.S Renal Disease System 2015 states that CVD was noted to be the common cause of mortality, accounting for 53% of all deaths in patients with ESRD undergoing HD (21). The study data showed that increasing age and obstructive uropathy were significant predictors that affected the development of cardiovascular events in patients.

This study also demonstrated that the rates of developing new cardiovascular events were significantly higher in patients with ESRD undergoing HD who were aged 45-64 years and ≥65 years than in younger patients. This finding in agreement with those reported in studies conducted in the US, which documented that older age was an important traditional risk factor for the development of cardiovascular events among patients undergoing HD (7, 10, 21). This may

**Table 2.** Clinical characteristics of 534 patients with anemic ESRD undergoing hemodialysis

Variable	n (%)
<b>Comorbidities</b>	
Others diseases	67 (12.5)
Gout	55 (10.3)
No comorbid disease	47 (8.8)
Hyperlipidemia	21 (3.9)
Liver disease	10 (1.9)
Postoperative complication	7 (1.3)
Malnutrition	1 (0.2)
<b>Etiology of ESRD</b>	
Hypertension	297 (55.6)
Diabetes mellitus	135 (25.3)
Obstructive uropathy	79 (14.8)
Other causes	81 (15.2)
Treatment	40 (7.5)
Unknown	37 (6.9)
Chronic glomerulonephritis	37 (6.9)
Pyelonephritis	37 (6.9)
Interstitial nephropathy	6 (1.1)
Hereditary nephropathy	3 (0.6)

ESRD: end-stage renal disease

be explained by the fact that older patients are more vulnerable to HTN or other CVD risk factors than younger patients, despite HTN being a leading cause of ESRD in both age groups. Likewise, a previous Sudanese study documented that HTN and DM were more significant baseline causes of ESRD in elderly patients than in younger patients (22). HTN is the most important risk factor for stroke and coronary heart disease among the Sudanese general population (23). In contrast, a recent meta-analysis by Hallan et al. (24) found that among patients with ESRD, older age was associated with lower risks for CVD than younger age. Moreover, HTN and age were associated with CVD in patients undergoing HD and continuous ambulatory peritoneal dialysis (25). The results of the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial showed that higher risks for morbidity and mortality owing to cardiovascular events among older patients with CKD and higher Hb levels, were in agreement with the results of the current study (26).

Furthermore, in this study, obstructive nephropathy was predictive of enhanced cardiovascular events in patients undergoing HD. This finding in agreement with a previous study by Rule et al. (27) that kidney stone was a significant predictor of myocardial infarction in patients with CKD, which increased the risk for CVD. This may be explained by the fact that obstructive uropathy was found to be the second primary cause of ESRD in Sudan, which may be associated with dietary habits and a higher prevalence of uncontrolled HTN and urinary schistosomiasis, as well as with aggravated CVD owing to ESRD accompanied with anemia and traditional risk factors for CVD such as DM, HTN, dyslipidemia, and smoking (28).

The results of this study are similar to those of previous studies, which found that kidney stones was predictive of a higher risk for chronic heart disease, atherosclerosis, and stroke (29, 30). Similarly, the current findings are in agreement with those of a recent study, which showed that non-Hispanic blacks with kid-

**Table 3. Factors affecting the development of cardiovascular events using logistic regression analysis**

Variable	Odds ratio (95% confidence interval)	
	Unadjusted	Adjusted
<b>Sex</b>		
Male vs. Female	1.02 (0.70-1.49)	
<b>Age (years)</b>		
18-44	1	1
45-64	1.78 (1.09-2.88)*	-
≥65	9.46 (5.42-16.51)**	6.11 (3.66, 10.18)**
<b>BMI (kg/m<sup>2</sup>)</b>		
Underweight (<18.5)	1	
Normal weight (18.5-24.9)	1.53 (0.96-2.44)	
Overweight (≥25)	1.72 (0.55-5.45)	
<b>Insurance status</b>		
Uninsured vs. Insured	1.45 (0.99-2.13)	1.51 (0.98, 2.32)
<b>Education level</b>		
≥secondary vs. <secondary	2.16 (1.47-3.17)**	1.55 (0.99, 2.43)
<b>Smoking habit</b>		
Non-smoking vs. smoking	1.15 (0.79-1.67)	
<b>Alcohol intake</b>		
Non-alcoholic vs. alcoholic	0.89 (0.55-1.44)	
<b>Family history of ESRD</b> (No/Yes)	0.96 (0.60-1.55)	
<b>Comorbidities</b>		
Past medical history (Yes/No)	2.47 (1.08-5.64)*	
Liver disease (No/Yes)	1.06 (0.27-4.15)	
Gout (No/Yes)	1.91 (1.08-3.38) *	1.88 (0.98, 3.61)
Hyperlipidemia (No/Yes)	1.55 (0.63-3.81)	
Postoperative complication	0.99 (0.19-5.14)	
Others (No/Yes)	0.75 (0.41-1.36)	2.51 (1.15, 5.48)*
<b>Etiology of ESRD</b>		
Hypertension (No/Yes)	2.02 (1.36-2.99)**	1.75 (1.10, 2.79)*
Diabetes mellitus (No/Yes)	1.60 (1.05-2.42)*	
Glomerulonephritis (No/Yes)	0.56 (0.24-1.29)	
Obstructive uropathy (No/Yes)	1.63 (0.99-2.69)	2.61 (1.47, 4.66)*
Pyelonephritis (No/Yes)	1.20 (0.59-2.45)	
Interstitial nephropathy (No/Yes)	0.49 (0.06-4.23)	
Treatment (No/Yes)	3.02 (1.16-7.87)*	2.84 (0.88, 9.15)
Other diseases (No/yes)	1.20 (0.72-1.99)	
Unknown (No/Yes)	0.56 (0.24-1.29)	

\*p<0.05, \*\*p<0.001, a model adjusted for all the above variables; BMI: body mass index; ESRD: end-stage renal disease

ney stones have an increased 10-year risk for an atherosclerotic cardiovascular disease event, as determined using the Pooled Cohort Equations (31). Further evidence was provided that nephrolithiasis and atherosclerosis share common systemic risk factors and/or pathophysiology (32). However, the majority of kidney stones in ESRD may relate to calcium and/or calcium oxalate. Which is similar to the pathophysiology of vascular plaque, that owing to vascular calcification by the deposition of calcium in blood vessel leading to CVD (33). Moreover, kidney stone and CVD may be associated with higher levels of uric acid, which

**Table 4. Factors substantially affecting the development of cardiovascular events using multiple logistic regression analysis**

Variable	β <sup>a</sup>	Adjusted OR (95% CI)	p
<b>Sociodemographic factors</b>			
<b>Age groups (years)</b>			
18-44	0	1	
45-64	0.66	1.94 (1.18-3.18)	0.009
≥65	2.39	10.88 (6.12-19.33)	<0.001
<b>Clinical factors</b>			
<b>Obstructive uropathy</b>			
No	0	1	
Yes	0.84	2.33 (1.34-4.03)	0.003

ESRD: end-stage renal disease

acts as a proinflammatory agent, leading to the elevation of C-reactive protein levels and endothelial dysfunction (34).

The association between nephrolithiasis and CVD may be owing to the dietary intake of minerals such as calcium, sodium, and potassium, as well as owing to overweight and higher consumption of animal proteins; likewise, obstructive uropathy, the second leading cause of ESRD in Sudan, may be related to higher mineral dietary intake, body weight, higher consumption of animal protein, dietary habits, and population lifestyle (35, 36). In addition, the high prevalence of CVD risk factors such as HTN, DM, myocardial infarction, and stroke in patients with ESRD may have another explanation (37).

The limitation of this study was that the new cardiovascular events were recorded from the patients' medical history records during the follow-up period, and no further confirmation tests were done, as well as the study was observational study. The main strengths of this study are its prospective nature and utilization of a large sample size.

In conclusion, this study revealed that advanced age and obstructive uropathy were important factors that were more likely to influence the development of cardiovascular events among patients with ESRD undergoing HD. Therefore, more concern should be shown for elderly patients and patients with obstructive uropathy to control and prevent cardiovascular events and to decrease morbidity and mortality rates, improve the quality of life, and reduce costs of anemia treatment. Moreover, controlling CVD risk factors such as HTN and DM is very important.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Research Ethics Committee, National Center for Kidney Diseases and Surgery, Ministry of Health, Khartoum, Sudan, 2012.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author contributions:** Concept - O.A., A.S.; Design - O.A., A.S.; Supervision - O.A., A.S., A.H., B.N.; Resource - O.A., A.S.; Materials - O.A.; Data Collection and/or Processing - O.A.; Analysis and /or Interpretation - O.A., A.S., A.H., B.N.; Literature Search - O.A.; Writing - O.A.; Critical Reviews - O.A., A.S., A.H., B.N.

**Acknowledgements:** Authors would like to thank University Sains Malaysia (USM) for awarding the fellowship for this research for the last year. Many thanks to the staffs and patients in hemodialysis centers, Khartoum state, for their contribution in this study.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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