

# The impact of vascular calcification among dialysis dependent south African CKD patients: A five year follow up study.

## *Cardiovascular mortality and morbidity, ethnic variation and hemodynamic correlates*

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# Abstract

**BACKGROUND** Vascular calcification is a risk factor for cardiovascular morbidity and mortality in patients with end stage renal disease (ESRD). In Western countries, Blacks with ESRD appear to have lesser degrees of vascular calcification compared to non-Blacks. However, there is no published data on the association of ethnic differences in vascular calcification and survival in ESRD from Sub-Saharan Africa.

**METHODS** This study assessed 5-year changes in vascular calcification and mortality in a previously published cohort of patients with ESRD. Vascular calcification was assessed by abdominal aortic calcification score and vascular stiffness by pulse wave velocity.

**RESULTS** Sixty-six of the original 74 participants, studied at baseline, were identified. The median age was 46.6 years (37.6-59.2) and 57.6% were women. Abdominal aortic calcification showed no progression among Blacks [baseline range 0-5, follow up range 0-8 ( $p=1.00$ )], but a non-significant trend to progression among non-Blacks [baseline range 0-19, follow up range 0-22 ( $p=0.066$ )]. Black participants did not display a survival advantage ( $p=0.870$ ). Overall, sepsis was the most common cause of mortality (64% of those with an identifiable cause of death). Non-Blacks had higher parathyroidectomy rates than Blacks with 9/30 cases compared to 2/36 ( $p=0.036$ ). After adjustment for parathyroidectomy at follow up, the odds ratio of having abdominal vascular calcification score of  $\geq 1$  amongst non-Blacks was 8.6-fold greater compared to Blacks ( $p=0.03$ ). Central aortic systolic pressures (CASP) and pulse wave velocities (PWV) were higher in the study population than age matched normative values. At follow up, a positive correlation ( $r=0.5$ ) was observed between PWV and abdominal aortic calcification ( $p=0.047$ ). Elevated baseline coronary artery calcification score and FGF-23 level at baseline were not associated with a difference in mortality.

**CONCLUSION** There was no significant progression in vascular calcification among Blacks. After adjusting for increased parathyroidectomy rates, there was a greater progression of vascular calcification amongst non-Blacks compared to Blacks highlighting possible ethnic differences in calcium phosphate metabolism in patients with ESRD. Lack of vascular calcification progression in Blacks was not associated with improved survival, but the sample size was small.

## Background

Chronic Kidney Disease (CKD) is a major public health problem in South Africa (SA) due to the high prevalence of hypertension, diabetes and HIV.<sup>1,2,3</sup> A population based sample study conducted in Bellville, Cape Town using the Modification of Diet in Renal Disease (MDRD) equation to calculate the estimated glomerular filtration rate, demonstrated a high prevalence of CKD stage 3 - 5 of 7.6% (with ethnicity correction) and 23.9 % (without ethnicity correction).<sup>4</sup> CKD has a higher cardiovascular(CV) mortality due to traditional risk clustering of CV as well as non-traditional CV risk factors, including vascular calcification of the tunica media.<sup>5</sup>

Various surrogate markers have been used to assess vascular health in patients with CKD.<sup>6</sup> The extent of coronary artery calcification has shown to be a powerful clinical predictor of long term prognosis in asymptomatic CKD patients.<sup>7</sup> Furthermore, Fibroblast Growth Factor 23 (FGF-23) is positively associated with left ventricular hypertrophy (LVH), endothelial dysfunction, progression of CKD and a higher mortality.<sup>8,9</sup> Pulse wave velocity (PWV) and central aortic systolic pressure (CASP) can be used non-invasively to measure vascular health.<sup>9</sup> In CKD, regardless of the stage, patients have higher PWV level compared to controls with preserved renal function.<sup>10</sup> Blacher et al<sup>11</sup> showed that, in patients with ESRD, increased PWV was a strong independent predictor of CV and all-cause mortality. Vascular calcification, atherosclerosis, changes in collagen and elastin, and uremia are all thought to result in increased arterial stiffness in CKD.<sup>12</sup>

Ethnicity may also play a role in the development of vascular calcification. Numerous studies in developed countries describes slower progression of vascular calcification in Blacks compared to non-Blacks.<sup>13,14</sup> Freercks et al<sup>15</sup> showed that Black South African dialysis patients appeared to be protected from vascular calcification. The median coronary calcium score among Blacks was 0 (IQR 0) and 66 non-Blacks (IQR 383 p < 0.01)<sup>15</sup>. Even after adjustment, Black race remained a negative predictor for coronary calcification<sup>15</sup>. There is a paucity of other data on ethnic variations in vascular calcification in sub-Saharan Africa. This apparent advantage for Blacks on dialysis may be due to a lower pro-inflammatory state, dietary intake, genetic factors and variations in bone mineral metabolism.<sup>7,10,16</sup> Differences in ethnic bone mineral metabolism regulation, bone mass acquisition and architecture are well described.<sup>16-22</sup> Black subjects with end stage renal disease (ESRD) have been shown to have a more favorable bone density and bone architecture, less calcium renal excretion, elevated gastrointestinal calcium absorption, lower 25-hydroxy vitamin D and higher levels of parathyroid hormone (PTH) than their non-Black counterparts.<sup>17,18,19</sup>

The present study is a five year follow up, single centre study of patients initially recruited to investigate vascular calcification in dialysis-dependent patients.<sup>15</sup> The study aimed to assess the progression of vascular calcification and ensuing clinical sequelae as well as the possible survival advantage of Blacks on dialysis. The study protocol was approved by the Human Research Ethics Committee of the University of Cape Town (HREC REF: 048/2016).

## Methods

Of the 74 patients recruited in the initial study, 66 were traced. All study participants were over 18 years old and provided written informed consent. Testing was conducted on the dialysis patients after completion of dialysis and on pre-scheduled clinic appointment visits in non-dialysis dependent patients. The cohort's study methods have been described in detail elsewhere<sup>20</sup>, but included: baseline anthropometry, electrocardiogram (ECG), abdominal calcification scores (calculated from lateral abdominal radiograph), coronary calcium scores (CCS) calculated from a cardiac computer tomography, and FGF-23 levels. Medical data including smoking habits and dialysis modality were captured. The

following investigations were done at the 5-year follow-up visit: anthropometry, lateral abdominal radiograph, ECG, and PWV and CASP measurement using the AtCor Medical SphygmoCor XCEL® device.

All anthropometric measurements were conducted by one investigator (KS). The peritoneal dialysis patient was weighed after drainage of the dialysate. All haemodialysis patients had their weights measured post dialysis. Abdominal truncal obesity was defined using the African normative values of waist circumference of male  $\geq 94$  cm and females  $\geq 80$  cm.<sup>21</sup>

All resting ECGs were performed using standard calibration and analyzed by one investigator (SK). The Sokolow-Lyon (SL) and Cornell Criteria, as per European Society Cardiology guidelines, were used to diagnose left ventricular hypertrophy (LVH)<sup>22</sup> and were corrected for body mass index (BMI).<sup>23</sup>

Abdominal radiographs were taken using a standardized technique.<sup>15</sup> Scoring of calcification was assessed as per 24-point scale using the validated method described by Kaupilla et al.<sup>24</sup> The same investigator (RF) who conducted the abdominal calcification scoring in the initial study was blinded and scored all the radiographs done at follow up.

The data were entered into a RedCap database and cleaned using pivot tables in Microsoft Excel before being exported to STATA 14 (Stata Corp, College Station, Texas) for analysis. Statistical tests were performed according to whether the variable was continuous or categorical. Continuous data are expressed as mean values  $\pm$  SD or median values (IQR) depending on the normality of data. For categorical data the  $\chi^2$  test or Fisher exact test and the Z test were used to test for a statistical difference between variables and proportions, respectively. The Mann–Whitney and Student t test were used to test the association between continuous and categorical variables. Participants of African descent were classified as Blacks. The rest were classified as non-Blacks for analysis.

The survival of Blacks versus non-Blacks at 5 years was analyzed using Kaplan Meir curves. The difference in progression of vascular calcification among Blacks and non-Blacks at baseline and follow-up was analyzed using the paired t-tests and sign-rank paired test based on normality. PWV measurements were not undertaken in the initial study. Using normative values of PWV published in a South African study<sup>25</sup>, the effects of vascular calcification on PWV were identified. A BPro watch device (HealthSTATS, Singapore) was used to measure the CASP in the initial study. The five-year clinical outcome in relation to calcium scores at baseline was analysed using the Student's t-test.

## Results

Baseline and follow-up characteristics of the population are presented in table 1. At baseline and follow up 57.6% of participants were women (n = 38) and 54.5% were Black (n = 36). The majority of patients traced were still alive 63.6% (n = 42). Among participants that were alive: 57.1% (n = 24) had been transplanted, 40.5% (n = 17) were on hemodialysis and one patient was on peritoneal dialysis. Non-Blacks had progressive abdominal calcification approaching significance [baseline range 0–5, follow up

range = 0–8 ( $p = 0.066$ )] compared to Blacks who showed no progression [baseline range = 0–19, follow up range 0–22 ( $p = 1.00$ )]. Non-Blacks had higher parathyroidectomy rates of 9/30 cases compared to 2/36 cases of Black patients ( $p = 0.036$ ). The odds ratio of having abdominal vascular calcification score of  $\geq 1$  amongst non-Blacks at follow up was 8.6 fold greater than a similar calcification score amongst Blacks, after having adjusted for parathyroidectomy ( $p = 0.031$ ). At follow up, a positive correlation ( $r = 0.3$ ) was observed between PWV and abdominal vascular calcification ( $p = 0.04$ ). Significant weight gain among all participants at follow up compared to baseline was observed ( $27.1 \pm 7.1 \text{ kg/m}^2$  versus  $24.4 \pm 4.2 \text{ kg/m}^2$  respectively;  $p < 0.015$ ). There was a regression in LVH using both the SL score corrected for BMI ( $p < 0.001$ ) and Cornell product corrected for BMI ( $p = 0.027$ ). In our study group 12.1% ( $n = 4$ ) of transplanted patients during follow up developed new onset diabetes after transplantation (NODAT). Infections were the most common cause of morbidity (50.8%) followed by: ischemic heart disease (38.5%), gout (10.8%), NODAT (6.0%), peripheral vascular disease (3.1%), cerebrovascular accidents (3.1%), peripheral neuropathy (3.1%), depression (1.5%) and vertebral fractures (1.5%).

There was no difference in survival by ethnicity ( $p = 0.870$ ) (Figure 1). The renal replacement modality of participants who had died at follow-up included: 38% transplant ( $n = 9$ ), 16% peritoneal dialysis ( $n = 4$ ), 38% hemodialysis ( $n = 9$ ) and 8% had no data ( $n = 2$ ). Overall, sepsis was a major cause of mortality in our study group, seen in 9 of 14 participants (64%) in whom a cause of death could be identified. More participants with a  $\text{CCS} \geq 1$  at baseline were on dialysis than had been transplanted at follow up ( $p = 0.035$ ) (Table 3). Participants with coronary calcification had a higher numerical probability of dying (43.3% versus 30.6%;  $p = 0.213$ ).

### ***Table 1: Characteristics of the study population at baseline and follow-up***

CHARACTERISTIC	BASELINE (74)		FOLLOW-UP (66)		P-VALUE
AGE, median (IQR)	42.1 (32.7 – 49.3)		46.6 (37.6–59.2)		<0.0001 °
WOMEN n, %	42 (56.8)		38 (57.6)		0.922 †
BLACKS n, %	40 (54.1)		36 (54.5)		0.954 †
<b>RENAL REPLACEMENT STATUS, n (%)</b>					
HD			28 (42.4)		
PD			5 (7.6)		
Transplant			33 (50.0)		
<b>ALIVE, n (%)</b>					
All			42 (63.6)		
HD			17 (40.5)		
PD			1 (2.4)		
Transplant			24 (57.1)		
<b>BMI</b>					
All	24.3 (±4.1)		27.1 (±7.1)		0.015 ‡
Transplanted	24.6 (±3.4)		27.4 (±8.3)		0.100 ‡
Dialysis	24.1 (±4.7)		26.6 (±5.1)		0.008 ‡
<b>DM INCIDENCE</b>					
All			4 (6.0)		
Transplant			4 (12.1)		
Dialysis			0		
Blacks			4 (11.1)		0.131 †
Non-Blacks			0		
<b>ABDO CALC (mean, SD)(mode)</b>					
Blacks	0.4 (±1.3)	0 - 5	0.6 (±1.9)	0 - 8	1.000 ‡
Non-Blacks	4.9 (±7.1)	0 - 19	5.6 (±6.9)	0 - 22	0.066 ‡
<b>LVH</b>					
SL Score corrected for BMI (mm*kg,m <sup>2</sup> )	939 (±376)		671 (±280)		<0.001 ‡
SL Score corrected for BMI Blacks	926 (±364)		696 (±334)		0.068 ‡
SL Score for BMI Non-Blacks	954 (±407)		666 (±215)		0.002 ‡

° Mann-Whitney U test

‡ Student's t-test

† Z-test

0255075100Proportion of patients with the outcome of death (%)3027(3)26(1)24(2)21(3)19(2)ethnicity = non-black3635(1)32(3)30(2)27(3)22(3)ethnicity = blackNumber at risk012345

Analysis time (years)

BlacksNon-blackslog rank p-value = 0.870Kaplan-Meier estimates for patients who died at follow-up according to race 000255075100Proportion of patients with the outcome of death (%)3027(3)26(1)24(2)21(3)19(2)ethnicity = non-black3635(1)32(3)30(2)27(3)22(3)ethnicity = blackNumber at risk012345  
Analysis time (years)

BlacksNon-blackslog rank p-value = 0.870Kaplan-Meier estimates for patients who died at follow-up according to race *Figure 1: Kaplan–Meier estimates of patients who had died at follow-up according to race*

All females and 85% of male participants had truncal obesity at follow up.<sup>21</sup> The median abdominal circumference of males was 96.5cm (IQR: 93–102.5cm), 2.7% above the African normative values. Females had a median abdominal circumference of 101.5cm (IQR: 90 –108 cm), 27% above normative African values. There was no difference in abdominal obesity between Blacks and non-Blacks (p = 0.254). The median BMI at follow up for participants who developed NODAT was 23.4kg/m<sup>2</sup> (19.5–27.2) compared to those who did not develop NODAT 27.5kg/m<sup>2</sup> (23.7–31.4) (p = 0.095). A mean weight gain of 1.1kg (1.5) was observed among participants who developed NODAT compared to 4.8kg (3.4) (p = 0.072) in participants who did not develop NODAT. In our study group, only Black participants developed NODAT (Table 1).

At baseline non-Blacks had a higher numerical median FGF–23 compared to Blacks (p = 0.513). Study participants who had higher FGF–23 at baseline had a higher probability of death that approached significance (p = 0.075). FGF–23 could not be measured at follow up.

Using normative values among an age-stratified South African population, higher median values of PWV were observed among participants in the age groups below 60 years compared to normative values (Table 2).<sup>24</sup> A positive correlation between PWV and abdominal calcification was observed at follow up (r = 0.5, p = 0.047) Baseline CASP was not a predictor of outcome at follow up, baseline mean CASP was 134.5mmHg (±24.1) for participants alive at follow up compared to baseline CASP of 132.1mmHg (±29.2) in those who had died at follow up (p = 0.723).

***Table 2: Pulse wave velocity at follow up compared to African normative values***

Pulse wave velocity	Normative Values <sup>24</sup>		Participants	
	Males & Females	Value 50 <sup>th</sup> (10 <sup>th</sup> 90 <sup>th</sup> )	Value 50 <sup>th</sup> (n)	(10 <sup>th</sup> 90 <sup>th</sup> )
20-29 years		6.1 (5.3, 7.10)	6.6 (7)	(5.3, 8.6)
30-39 years		6.4 (5.2, 8.00)	7.3 (7)	(4.9, 13.1)
40-49 years		6.9 (5.9, 8.60)	8.1 (14)	(6.3, 10.4)
50-59 years		8.1 (6.3, 10.0)	8.8 (5)	(6.5, 12.3)
60-69 years		10.3 (9.7, 13.1)	8.1 (1)	

**Table 3: Patient characteristics at follow up, stratified by baseline coronary calcium scores (CCS)**

CHARACTERISTIC	CCS = 0	CCS ≥ 1	P-VALUE
<b>Current status, n (%)</b>			
Haemodialysis	12/36 (33.3)	15/27 (55.6)	0.015 ®
Peritoneal dialysis	1/36 (2.8)	4/27 (14.8)	
Transplant	23/36 (63.9)	8/27 (29.6)	
<b>Vital status, n (%)</b>			
Alive	25/36 (69.4)	14/27 (51.9)	0.155 ¥
Dead	11/36 (30.6)	13/27 (48.1)	
<b>Complications, n (%)</b>			
Cardiovascular diseases	14/36 (38.9)	16/30 (53.3)	0.241 ¥
Parathyroidectomy	4/36 (11.1)	5/30 (16.7)	0.721 ®
Gout	3/36 (8.3)	4/30 (13.3)	0.511 ®
Infections	16/36 (44.4)	17/30 (56.7)	0.323 ¥
Peripheral neuropathy	1/36 (2.8)	1/30 (3.3)	
Depression	1/36 (2.8)	0	-
Vertebral fracture	1/36 (2.8)	1/30 (3.3)	-
<b>SL score corrected for BMI, mean (±SD)</b>	<b>720.3 (±336)</b>	<b>625.1 (±193)</b>	<b>0.289 ‡</b>

‡ Student's t-test, ¥ Chi-square, ® Fishers exact test

## Discussion

To our knowledge, this is the first follow up study in sub-Saharan Africa assessing the progression of vascular calcification among ESRD patients. Due to resource limitations, stringent criteria are applied to assess eligibility for state funded dialysis and subsequent transplantation. For example, patients >60 years and diabetics >50 years, morbidly obese patients and diabetics with significant target organ disease are not accepted. This explains our relatively young, non-diabetic, non-obese study population (Table 1).

In this study we found that non-Black patients had a trend to greater progression of vascular calcification. While the sample size is small, this is consistent with numerous studies in the developed world that have shown that ethnicity is a risk factor for the progression of vascular calcification with slower progression among Blacks.<sup>26,27</sup>

Blacks in our study group had lower parathyroidectomy rates. However, studies in the USA have found higher parathyroidectomy rates among Blacks compared to non-Blacks.<sup>28,29</sup> This contrary finding is not explained and could be confounded by the small sample size.

BMI significantly increased during the study period, likely due to the effects of transplantation as well as improved nutrition after the continuation of effective dialysis and amelioration of uremic symptoms. All females and 85% of males met African criteria for abdominal obesity.<sup>21</sup> Obesity is regarded as a risk factor for cardiovascular disease, reduced patient survival, graft rejection and loss as well as death among patient's organ transplant recipients.<sup>30,31,32</sup> NODAT developed in 12.1% of the patients who had received a kidney transplant and they were all Black ( $p = 0.131$ ). This finding is consistent with published data where NODAT has been reported to occur in 2–53 % of all solid organ transplants and is a serious and common complication of kidney transplantation.<sup>33 34</sup> In our group, weight gain was not a risk factor of developing NODAT: 1.1kg ( $\pm 1.5$ ) vs 4.8kg ( $\pm 3.4$ )  $p = 0.072$ . Known risk factors for developing NODAT are multifactorial and include race, age of recipient, male sex, family history of diabetes mellitus, genetics, rejection history and type of immunosuppressant therapy prescribed.<sup>33</sup>

LVH is a poor outcome predictor among patients on hemodialysis and in transplant patients.<sup>35,36</sup> The significant regression in LVH among dialysis and transplant patients at follow up could possibly be ascribed to BP control and management of hyperparathyroidism.<sup>37,38</sup> Left ventricular remodeling is thought to occur after renal transplant, effecting systolic and diastolic function, but the evidence is not uniform.<sup>39</sup> After a follow up of 2 years, Rajan et al observed that kidney transplant had no association with significant regression of left ventricular mass index using cardiac magnetic resonance imaging compared to patients on the waiting list.<sup>40</sup> However, others report that renal transplant is associated with significant LVH regression.<sup>41, 42</sup> The LVH regression among our study participants was not found to be solely due to renal transplantation.

Studies in the developed world have shown a 'survival paradox' in Blacks compared to non-Blacks.<sup>43,44,45</sup> We did not find a difference in survival in Blacks in our cohort despite the absence of progressive vascular calcification in them. Recent studies in the USA have suggested that this apparent survival advantage is less significant in age groups above 40 years.<sup>14</sup> A larger sample size would be needed to accurately assess this possible survival advantage in our predominantly young, Black African dialysis population. However, among participants with a known cause of death, the majority died of sepsis (64%) which is consistent with studies done in Brazil and sub-Saharan Africa.<sup>46, 47</sup> This is likely to have obscured any difference attributable to cardiovascular causes.

High levels of vascular stiffness are associated with CKD and dialysis dependency<sup>48, 49</sup>. Higher PWV values in participants at follow up, compared to available normative age-stratified ranges, were found.

The study should be viewed in the context of its potential limitations. The sample size is small and medical data was collected from patient files thus some data could have been missing or not documented. The selection criteria for participation in the state dialysis program is rigorous due to limitation of resources and most patients are from a low-socio economic background; this could affect the replicability of these results in other cohorts<sup>50</sup>. Although it was a single center study this was a longitudinal study with a strong follow up rate of 87.8%. The same investigators assessed certain clinical parameters at baseline and follow up which included abdominal X-rays and ECGs to reduce inter-observer variability.

## Conclusion

In conclusion, the study describes a majority of less than 50 years old, Black, ESRD population in a resource constrained setting. Increased vascular stiffness and metabolic risk factors, were highlighted and sepsis was a major cause of death among all participants. The differences in coronary calcification progression and parathyroidectomy rates between Blacks and non-Blacks suggest ethnic variances in mineral metabolism among patients with ESRD. Further research, in a larger cohort, is needed to understand these differences and inform and improve management of all patients with CKD.

## Abbreviations

BMI : Body Mass Index

CASP: Central Aortic Systolic Pressure

CCS : Coronary Calcium Scores

CKD : Chronic Kidney Disease

CV: Cardiovascular

ECG: Electrocardiogram

ESRD:End Stage Renal Disease

FGF 23 : Fibroblast Growth Factor 23

HIV: Human Immunodeficiency Virus

LVH : Left Ventricular Hypertrophy

MDRD: Modification of Diet in Renal Disease

NODAT : New Onset Diabetes after Transplantation

PWV: Pulse Wave Velocity

SA: South Africa

STATA 14: Stata Corp, College Station, Texas

## Declarations

*Ethics approval and consent to participate:* The study protocol was approved by the Human Research Ethics Committee of the University of Cape Town (HREC REF: 048/2016).

*Consent for publication :* Not Applicable.

*Availability of data and material :* The Dataset is available on ZivaHub Open dataUCT

*Competing interests :* Not Applicable

*Funding* Not Applicable

*Authors' contributions*

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## Figures

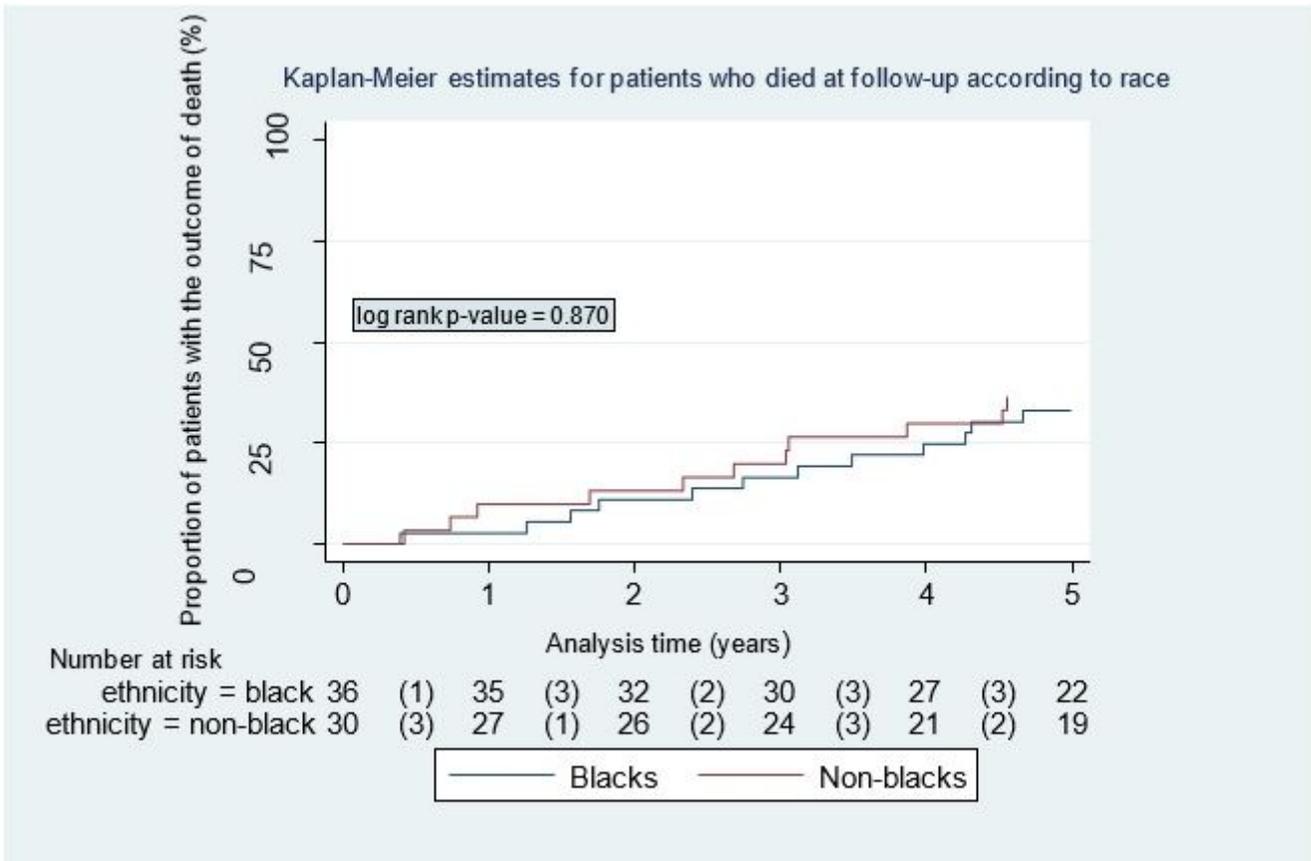


Figure 1

Kaplan – Meier estimates of patients who had died at follow-up according to race