

Ventricular Hypertrophy and Cardiovascular Mortality in Hemodialysis Patients With Low Educational Level

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Abstract

Background: Left ventricular hypertrophy is a strong predictor of mortality in chronic kidney patients. A previous study of our group has shown that chronic kidney patients with low educational level has more severe ventricular hypertrophy.

Objective: To extend a previous study and to assess whether left ventricular hypertrophy can explain the association between schooling and cardiovascular mortality in hemodialysis patients.

Methods: This study assessed 113 patients from January 2005 to March 2008 and followed them up until October 2010. Survival curves were built to compare all-cause and cardiovascular mortality of patients with up to three years of schooling (median schooling) and those with schooling of four years and over. Cox multiple models were built and adjusted to confounding variables.

Results: Association between educational level and ventricular hypertrophy was observed. Statistical difference in all-cause and cardiovascular mortality between the different educational levels was observed at 5.5 years of follow-up. In the Cox model, ventricular hypertrophy and C-reactive protein associated with all-cause and cardiovascular mortality. The etiology of kidney failure associated with all-cause mortality, and creatinine associated with cardiovascular mortality. The association between educational level and mortality lost statistical significance in the adjusted model.

Conclusion: The results of this study confirm those of a previous study. In addition, they show that the higher cardiovascular mortality observed in patients with low educational level can be explained by risk factors of biochemical and cardiac morphological origin. (Arq Bras Cardiol 2012;98(1):52-61)

Keywords: Hypertrophy, left ventricular/mortality, renal dialysis, underachievement, kidney diseases.

Introduction

The less fortunate portion of the population has low life expectancy, which is associated with the accumulation of cardiovascular risk factors¹. Socioeconomic indicators are related to the prevalence and severity of arterial hypertension^{2,3}. When assessing the association between arterial hypertension and low educational level, the causal nexus between those variables is likely to be income, and not educational level. However, a Brazilian study including educational level and income as independent variables in a multiple regression model has shown that educational level and not income⁴ was the factor associated with blood pressure increase.

Blood pressure is the major determinant of left ventricular hypertrophy (LVH). Thus, LVH would be expected to be also more severe in individuals with lower educational level and income. Rodriguez et al⁵ have reported an association between educational level and left ventricular mass in individuals living in the city of Nova York. Among white individuals, that association resulted from the higher blood pressure levels observed in individuals with lower educational level; however, among black individuals, the effect of the educational level on LVH did not depended on blood pressure increase. In a Brazilian study, lower socioeconomic status was associated with a higher salt intake⁶. Excessive salt consumption also causes left ventricular enlargement independent of blood pressure⁷, which could also explain the findings of Rodriguez et al⁵.

In the general population, the lower the socioeconomic status, the higher the mortality, regardless of confounding factors^{8,9}. Thus, there is evidence that low socioeconomic status is associated with higher morbidity and mortality. It is worth emphasizing that such association is also specifically observed in chronic kidney disease (CKD).

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Cardiovascular diseases are the most frequent causes of morbidity and mortality in end-stage CKD patients^{10,11}. Left ventricular hypertrophy, not only in the general population, but also in the dialysis population, is a strong predictor of cardiovascular events. On the other hand, arterial hypertension is the major pathogenic factor of ventricular hypertrophy both in the general¹² and CKD population^{13,14}.

In a previous cross-sectional study performed in our institution with 79 CKD patients undergoing hemodialysis, an educational level of a maximum of three school years was associated with more marked ventricular hypertrophy. That association did not depend on the arterial hypertension severity^{15,16}.

In hemodialysis patients, life expectancy is extremely reduced and, similarly to that which occurs in the general population, the socioeconomic status also influences mortality. There is an additional significant reduction in the life expectancy of those patients as their educational level decreases¹⁷⁻²⁰. In Brazil, only one study²¹ has assessed the impact of the educational level on the mortality of hemodialysis patients and on cardiovascular mortality. An assessment of how LVH and arterial hypertension could explain the association between the educational level and cardiovascular outcomes in CKD could be found in neither national nor international literature. Thus, this study aimed at extending a previous cross-sectional study and at assessing in a longitudinal study whether LVH and arterial hypertension could justify the association between educational level and cardiovascular mortality in hemodialysis patients.

Methods

This study is an observational longitudinal cohort, part of a doctorate dissertation, an extension of a previous cross-sectional study^{15,16}. All patients over the age of 18 years undergoing chronic hemodialysis at the Hospital das Clínicas of the Medical School of Botucatu (UNESP), in the city of Botucatu, state of São Paulo, were eligible for this study. Of the 141 patients assessed, 28 were excluded, leaving for analysis 113 hemodialysis patients undergoing echocardiography from January 2005 to March 2008. A standardized questionnaire on socioeconomic characteristics was completed by the 113 patients, who were followed up until October 2010. Patients who refused to participate were excluded, as were those who lacked intellectual ability to answer the questionnaire. These patients' medical care, however, was not jeopardized. In addition, patients with the following echocardiographic characteristics were excluded: unsatisfactory echocardiography due to poor left ventricular visualization; evidence of heart valve disease; and segmentary left ventricular kinetic alterations.

The sample size (113 patients) is sufficient to detect a 26% statistical difference in mortality in five years, assuming that the mean annual dialysis mortality is 16% and setting an 80% statistical power and $p < 0.05$.

This study was approved by the Research Ethics Committee of the Medical School of Botucatu (number 413/2008) and was conducted according to the resolution 196/96 of the Brazilian National Board of Health.

The sample was divided into two groups, according to the median of years of school attendance: G1, comprising patients with up to three years of schooling, representing a group without the minimum formal education (elementary school); G2, comprising patients with four or more years of schooling, representing a group with minimum formal education.

An interview was conducted with a standardized questionnaire on the following variables: age; gender; ethnicity; educational level (years of schooling); cause of CKD; monthly family income divided by the number of people in the household; and professional situation (working or inactive).

The following data were obtained from the patients' medical records and corresponded to the values obtained immediately before the 20 hemodialysis sessions prior to the echocardiography date: mean pulse rate; arterial blood pressure; and interdialytic weight gain. Body mass index was calculated by dividing weight by squared height (BMI, kg/m²).

The antihypertensive medications and laboratory and echocardiographic data were recorded. Left ventricular mass (LVM, g) was calculated according to the standardized formula and normalized to height to the power of 2.7 (left ventricular mass index - LVMI, g/m^{2.7})^{22,23}.

The continuous variables of normal distribution were compared between the groups by use of the *t* test for independent samples. The continuous variables of non-parametric distribution were compared by use of the Mann-Whitney test. The frequencies were compared by use of the χ^2 test or Fisher exact test, when indicated. Survival curves were built based on life tables and compared by use of the Greenwood's formula (Colton 1974). The initial date of the survival curves was considered that of the echocardiography. For the Cox multiple regression analysis, variables whose differences between the lower and higher schooling groups had a statistical probability lower than 10% were selected ($p < 0.1$). The primary outcome assessed was cardiovascular death, and the secondary outcome was all-cause death. Patients lost to follow-up at any date, those who underwent kidney transplantation, who recovered renal function, or who were alive by October 2010 were considered observation loss (censored) in the survival analyses. The risk of achieving the primary or secondary outcome was analyzed by using the Cox proportional hazard regression model with automatic selection of variables ("backward stepwise regression"). The model comprised only variables with statistical association at the 0.1 level. Data were expressed as mean \pm standard deviation or median (interquartile interval), when appropriate. The statistical significance level of $p < 0.05$ was adopted.

Results

Comparing the 113 patients assessed with the 28 excluded ones, no statistically significant difference regarding age, gender, ethnicity or educational level was observed.

Table 1 shows the sociodemographic variables in G1 and G2, which showed a statistically significant difference regarding age, educational level and income. The etiologies of kidney failure significantly differed between the groups ($p = 0.029$). Patients with a lower educational level had more hypertension and less glomerulopathies. The anti-hypertensive

drugs used showed no statistically significant difference between the groups.

Regarding the clinical variables (tab. 2), BMI showed a probability of statistical difference between G1 and G2 ($p = 0.077$). The other variables were homogeneous in both groups. The echocardiographic data (tab. 2) differed between groups regarding the following left ventricular characteristics: internal dimension ($p = 0.011$); relative thickness ($p = 0.049$); and mass index ($p = 0.020$).

A probability of statistical difference between groups lower than 0.1 was observed regarding the following laboratory data (tab. 3): fractional urea clearance ($p = 0.035$); creatinine ($p = 0.093$); hemoglobin ($p = 0.093$); pre-dialysis urea ($p = 0.072$); triglycerides ($p = 0.071$); and C-reactive protein ($p = 0.066$). In this case series, Kt/V values were as follows: lower than 1.2 in 26 patients (23%); between 1.2 and 1.4 in 39 (35%); between 1.4 and 1.6 in 22 (19%); and over 1.6 in 26 patients (23%).

The comparison of the all-cause mortality of patients with higher or lower educational level (fig. 1) shows that, from the third year of follow-up onwards, the curves begin to diverge. Up to five years and a half of follow-up, the probability of statistical difference between the groups is $p = 0.029$, with a higher number of events occurring among patients with lower educational level. The comparison of the cardiovascular mortality between the two groups with higher and lower educational level (fig. 2) shows that, from the third year of follow-up onwards, the curves begin to diverge. Up to five and a half years of follow-up, statistically significant difference occurs, with a higher number of events occurring among patients with educational level of three years or less ($p = 0.042$ at five years and a half). Table 4 shows the causes of death according to the educational level.

Figure 3 shows the relative risks of all-cause mortality by use of multiple analysis to assess the association between educational level and mortality. Including the confounding variables whose probability of statistical difference between the groups was lower than 0.1, the following were observed to associate with the risk of all-cause death independently from the confounding variables: LVMI; C-reactive protein; and other etiologies of CKD. In the final model, with automatic exclusion of the variables associated with

mortality with $p > 0.1$, LVMI (hazard ratio adjusted to confounding variables: 1.020; 95% CI: 1.005 – 1.035; $p = 0.007$) and C-reactive protein (hazard ratio adjusted to confounding variables: 1.573; 95% CI: 1.269 – 1.950; $p < 0.001$) were observed to associate independently with the risk for all-cause death. Other etiologies of renal failure than hypertension, diabetes and glomerulopathies associated with a lower risk of death ($p = 0.028$; relative risk of 0.158; 95% CI: 0.03 – 0.821). The higher pre-dialysis urea associated marginally with a lower risk of fatal outcome ($p = 0.052$; relative risk of 0.985; 95% CI: 0.971 – 1.000). The educational level did not associate with a higher risk for all-cause death in Cox multiple analysis.

Figure 4 shows the relative risks of cardiovascular death by use of multiple analysis to assess the association between educational level and mortality. Including the confounding variables with probability of statistical difference between the groups lower than 0.1, the LVMI and C-reactive protein were observed to associate with the risk for cardiovascular death independently of the confounding variables. The final model shows that, with automatic exclusion of the variables associated with mortality with $p > 0.1$, LVMI (hazard ratio adjusted to confounding variables: 1.035; 95% CI: 1.013 – 1.057; $p = 0.002$) and C-reactive protein (hazard ratio adjusted to confounding variables: 1.614; 95% CI: 1.089 – 2.393; $p = 0.017$) were directly and independently associated with the risk for cardiovascular death. Pre-dialysis creatinine (hazard ratio adjusted to confounding variables: 0.680; 95% CI: 0.511 – 0.904; $p = 0.008$) was inversely associated with the risk for cardiovascular death. The educational level did not associate with a higher risk for cardiovascular death in Cox multiple analysis.

Discussion

This study showed higher cardiovascular and all-cause mortalities in patients with lower educational level. However, when the confounding variables (biochemical and cardiac morphological changes) were considered, the educational level lost significance as a predictor of mortality. The major cause of death was that of cardiovascular origin. Thus, the higher mortality of patients with lower formal education was due to the cardiovascular and biochemical changes observed.

Table 1 – Demographic variables

	G1 (n=57)	G2 (n=56)	p
Age (years)	62 ± 11.9	53 ± 12.2	<0.001
Gender (F/M)	26/31	19/37	0.282
Ethnicity (W/NW)	41/16	32/24	0.148
Schooling (years)	1(0-2)	4(4-8)	<0.001
Income (R\$/person)	250(127-372)	371(233-500)	0.002
Dialysis (months)	28(11-62)	21(10-45)	0.339
Employed (y/n)	1/56	5/51	0.200

G1 - group with up to three years of schooling; G2 - group with minimum schooling of four years; F - female; M - male; W - white; NW - non-white.

The results of this study coincide with those of the previous study by the same group^{15,16}, as they confirm that patients with lower educational level had greater cardiac mass as compared with those of higher educational level in the extended case series. However, this study goes beyond, showing that the association between educational level and survival was mediated by ventricular changes. Another relevant finding was the association between higher LVMI and shorter survival, independently of the confounding variables, confirming, in the Brazilian case series, the findings of several international studies^{10,11}.

In accordance with the previous literature, the survival of hemodialysis patients was associated with the following biochemical variables: C-reactive protein²⁴⁻²⁶; urea²⁷; and creatinine²⁸.

A markedly low educational level was observed in the population studied, forcing the adoption of a low limit of years of school attendance as the criterion for dividing the groups: patients with up to three years of schooling (G1) and patients with at least four years of schooling (G2). The mean school

Table 2 – Clinical and echocardiographic variables

	G1 (n = 57)	G2 (n = 56)	p
SBPpre (mmHg)	142 ± 17.3	144 ± 17.1	0.673
DBPpre (mmHg)	85 ± 9.4	87 ± 9.0	0.195
HR (bpm)	76 ± 5.5	76 ± 4.1	0.765
BMI (g/m ²)	25 ± 4.3	24 ± 4.0	0.077
MIDWG (Kg)	2.3 ± 0.85	2.4 ± 1.00	0.326
PWTD	11.8 ± 2.24	12.2 ± 2.37	0.523
IVS (mm)	12.2 ± 2.29	12.5 ± 2.55	0.373
LVDD (mm)	50.6 ± 6.53	47.3 ± 7.33	0.011
LVRT (g)	0.25 ± 0.06	0.29 ± 0.09	0.049
LVMI (g/m ^{2.7})	82.3 ± 28.64	70.9 ± 22.12	0.020

G1 - group with up to three years of schooling; G2 - group with minimum schooling of four years; SBPpre - systolic blood pressure obtained immediately before dialysis; DBPpre - diastolic blood pressure obtained immediately before dialysis; HR - heart rate; BMI - body mass index; MIDWG - mean interdialytic weight gain; PWTD - posterior wall thickness in diastole; IVS - interventricular septum; LVDD - left ventricular diastolic diameter; LVMI - left ventricular mass index; LVRT - left ventricular relative thickness.

Table 3 – Laboratory variables

	G1 (n = 57)	G2 (n = 56)	p
Creatinine (mg/dL)	9.9 ± 3.37	11.0 ± 3.43	0.093
Calcium (mg/dL)	9.0 ± 0.82	9.2 ± 0.96	0.176
Phosphorus (mg/dL)	5.3 ± 1.74	5.5 ± 1.71	0.504
Glucose (mg/dL)	133 ± 64.9	131 ± 75.2	0.906
Bicarbonate (mEq/L)	21 ± 4.4	21 ± 3.1	0.501
Hb (g/dL)	11.5 ± 1.69	11.0 ± 1.57	0.093
Potassium (mg/dL)	50.1 ± 0.87	5.0 ± 0.92	0.661
Urea pre (mg/dL)	123 ± 32.5	134 ± 31.0	0.072
Ferritin (mg/dL)	512(301-918)	569(305-964)	0.789
Albumin (g/dL)	3.6 ± 0.33	3.6 ± 0.49	0.962
PTH (pg/mL)	220(108-498)	250(118-420)	0.576
Cholesterol (mg/dL)	147 ± 35.7	145 ± 39.9	0.727
Triglycerides (mg/dL)	159(115-223)	137(92-209)	0.071
Kt/V (adimensional)	1.4 ± 0.27	1.3 ± 0.27	0.035
CRP (md/dL)	0.95(0.30-1.95)	0.60(0.20-1.450)	0.066

G1 - group with maximum schooling of three years; G2 - group with minimum schooling of four years; Hb - hemoglobin; PTH - parathyroid hormone; Kt/V - fractional urea clearance; CRP - C-reactive protein.

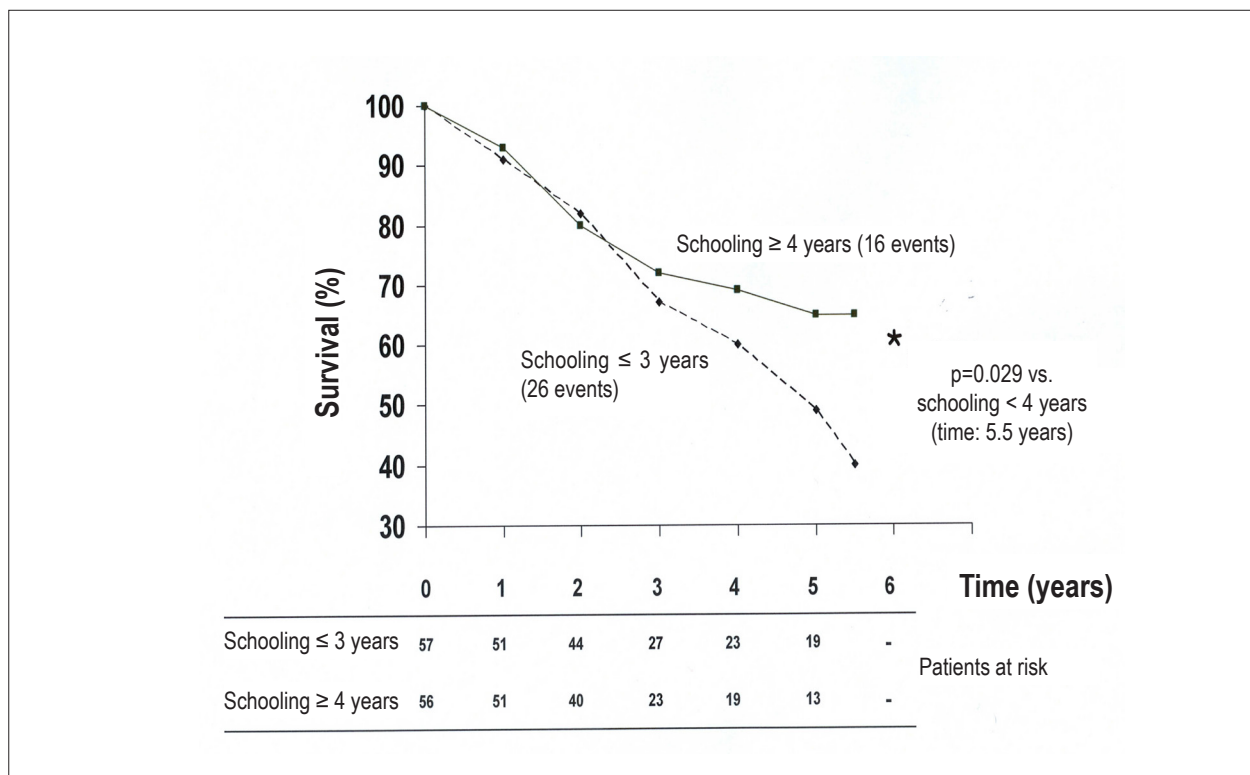


Figure 1 – All-cause mortality according to schooling of hemodialysis patients.

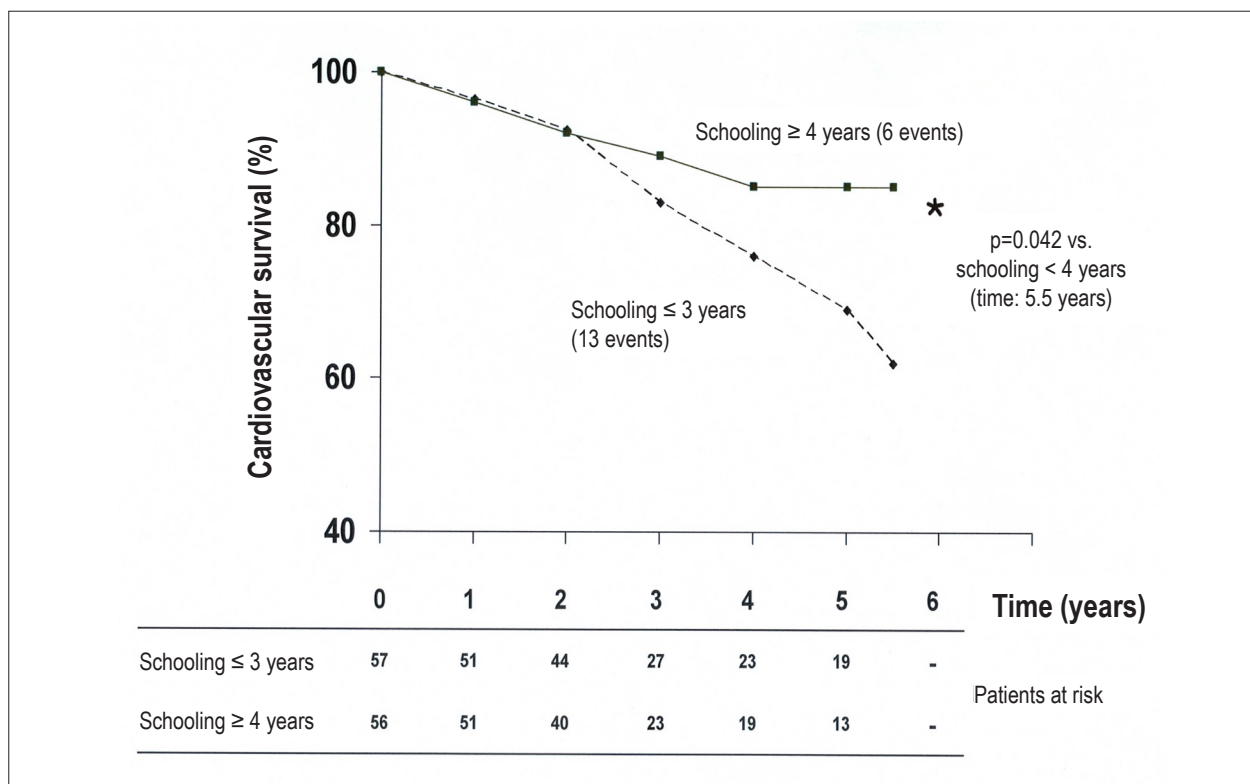


Figure 2 – Cardiovascular mortality according to schooling of hemodialysis patients.

attendance in this case series was 3.7 years. It is worth noting that the mean school attendance of Brazilians aged at least 15 years reached 7.5 years in 2009 (Portal Brasil, 2010)²⁹, being, thus, markedly greater than that of this case series (3.7 years).

In this study, patients with a lower educational level had higher cardiovascular and all-cause mortality. Considering the confounding variables, the effect of the educational level disappears, and ventricular hypertrophy and C-reactive protein remain as predictors of cardiovascular or all-cause mortality.

A study carried out in Brazil²¹ has reported a statistically significant association between low educational level (incomplete elementary education) and all-cause, but not cardiovascular, mortality in 334 hemodialysis patients. However, that association lost statistical significance in the multivariate model. Thus, those data are in accordance with this study's results, but they differ regarding the cause of death associated with low educational level: cardiovascular and all-cause mortality in this study and all-cause mortality in the above-cited study. In the international literature, the presence of low educational level has associated with a higher risk of death independently from the confounding variables^{30,31}. A possible explanation for the association between low educational level and mortality can be the poorer understanding of hemodialysis patients about CKD³².

In accordance with the literature, this study has found higher mortality among chronic kidney patients undergoing hemodialysis with higher LVM^{7,10,33}. The above-cited studies

have reported that patients with lower educational level have more cardiovascular disease. Thus, could cardiovascular changes explain the greater mortality of kidney patients with low educational level? Data of this study point to an affirmative answer.

In a study carried out in Brazil²¹, the all-cause and cardiovascular mortalities of hemodialysis patients did not correlate with the presence of LVH assessed on electrocardiography. In that study, 31% of deceased patients had LVH, while 35% of living patients had LVH detected on electrocardiography. Thus, no statistically significant difference was observed between the two groups. This showed that LVH assessed on electrocardiography could not foretell outcomes. The association between echocardiographic parameters and mortality obtained in the present study emphasizes the importance of performing echocardiography in hemodialysis patients.

Differently from that reported in the literature, the present study found no statistically significant relation between Kt/V and mortality. Two recent Brazilian studies are not in accordance with the present study^{21,34}. It is worth noting that, in the present case series, only 26 (23%) patients had Kt/V lower than 1.2. Thus, the relation between Kt/V and mortality might have been distorted by the presence of few patients with reduced Kt/V (lower than 1.2). In addition, patients with very high Kt/V might represent malnourished patients. It is worth noting that the total body water of patients with Kt/V lower than 1.2 was 37 ± 7.7 L; that of patients with Kt/V between 1.2 and 1.4 was

Table 4 – Causes of death according to schooling

	Schooling ≤ 3 years (n = 57)	Schooling ≥ 4 years (n = 56)
General causes		
Neoplasias	5	2
Sepsis	3	6
Trauma due to accident	1	0
Pneumonia	2	2
Acute abdomen	1	0
Digestive hemorrhage	1	0
Subtotal	13	10
Cardiovascular causes		
Acute myocardial infarction	2	1
Sudden death	5	2
APAO	1	0
Acute pulmonary edema	3	0
Stroke	2	1
Aorta aneurysm	0	1
Post-myocardial revascularization	0	1
Subtotal	13	6
Total	26	16

APAO - acute peripheral arterial occlusion.

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33 ± 6.1 L; that of patients with Kt/V between 1.4 and 1.6 was 30 ± 4.6 L; and that of patients with Kt/V greater than 1.6 was 27 ± 5.5 L (data not shown in results). This relation supports the hypothesis that high Kt/V was a marker of malnutrition, because it was related not to a higher Kt, but to a lower volume. Poorly nourished patients undergoing dialysis have the lowest volume and highest cardiovascular risk, corresponding to the malnutrition, inflammation and atherosclerosis (MIA) syndrome²⁴.

On multiple analysis, C-reactive protein and urea measured prior to dialysis were associated with all-cause mortality. Creatinine measured prior to dialysis and C-reactive protein showed a statistically significant association with cardiovascular mortality, independently from the confounding variables. In chronic kidney patients, inflammation is an important risk factor of mortality²⁴⁻²⁶. Thus, data of the present study support those of the literature.

Among hypertensives, there is usually a direct relation between creatinine level and cardiovascular mortality^{35,36}. The present study with dialysis patients showed an inverse relation between nitrogen waste products (urea and creatinine) and mortality, which is different from that of the general population,

but shows a behavior already documented in the literature^{27,28}. This fact should be explained considering that, in dialysis patients, urea and creatinine do not reflect renal function, which already is exiguous or inexistent, and pass to reflect protein intake and muscular mass, respectively (nutritional status). The results of the present study are compatible with MIA syndrome^{27,28}.

The present study showed that all-cause mortality was lower in patients whose renal failure cause was neither diabetes, nor arterial hypertension, nor glomerulopathies. Considering that the lower educational level group had more arterial hypertension as the cause of renal failure, that bias could explain, at least partially, the greater mortality of patients with lower educational level³⁷. In the present study, no statistically significant association was observed between renal failure etiology and cardiovascular mortality (p = 0.092). The smaller number of events with strictly cardiovascular origin might explain that divergence regarding all-cause mortality, which reduces the statistical power.

In conclusion, the higher cardiovascular mortality observed in patients with lower educational level could be explained by confounding factors of biochemical and cardiac morphological origin. Patients with lower educational level showed more

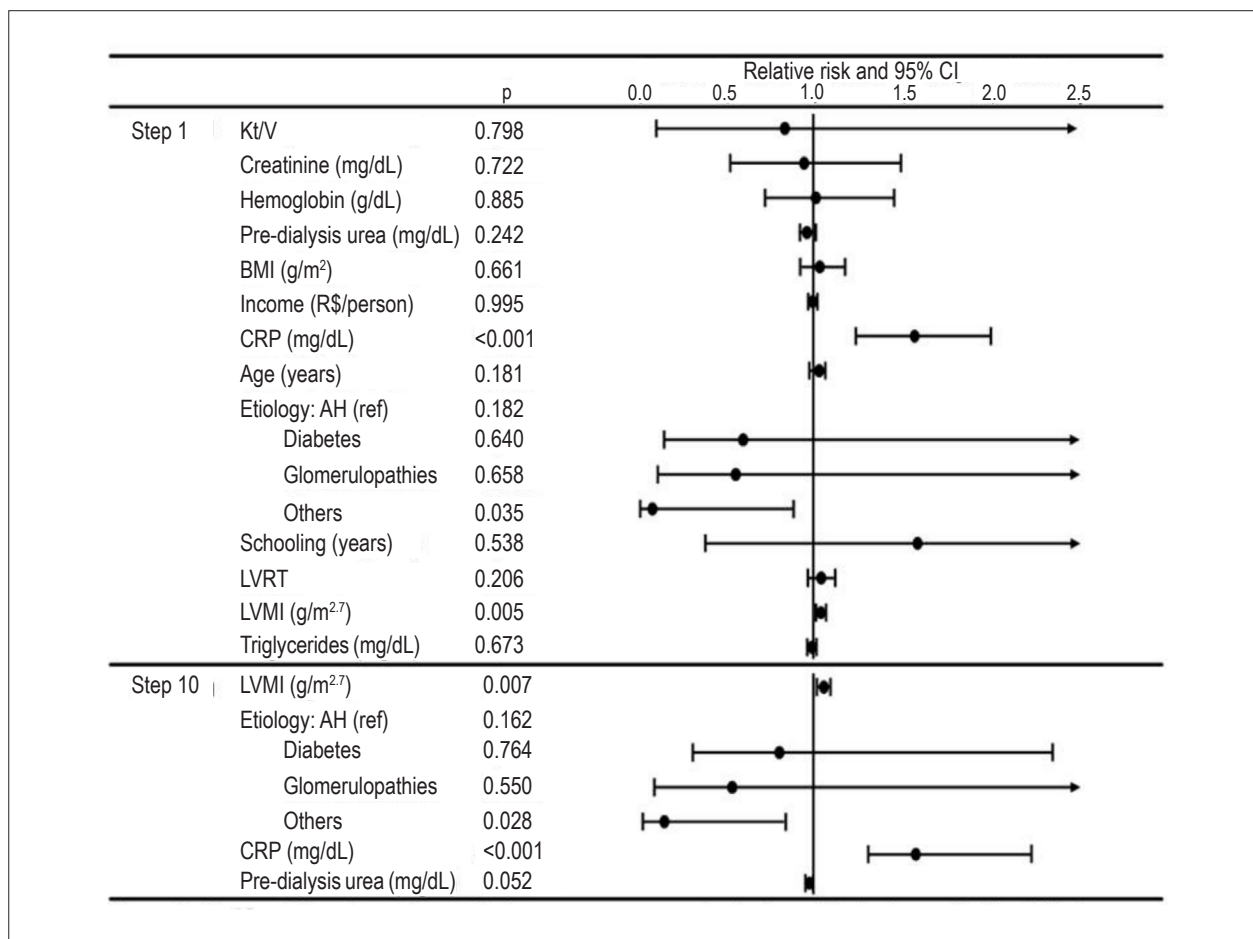


Figure 3 – Relative risk of all-cause death regarding confounding variables. Kt/V - fractional urea clearance; BMI - body mass index; Income - sum/individuals in household; CRP - C-reactive protein; AH - arterial hypertension; ref. - reference; LVRT - left ventricular relative thickness; LVMI - left ventricular mass index.

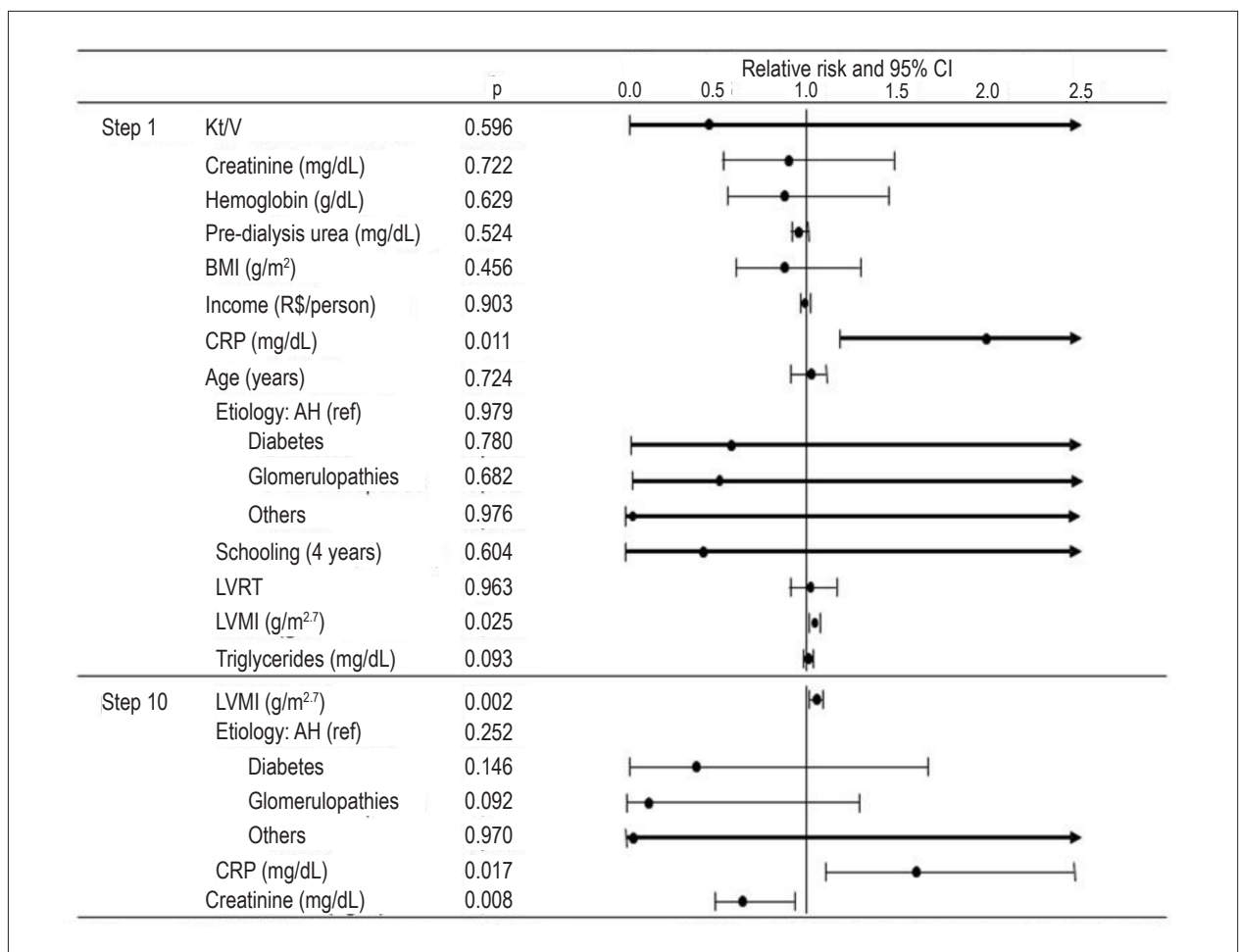


Figure 4 – Relative risk of cardiovascular death regarding confounding variables. Kt/V - fractional urea clearance; BMI - body mass index; Income - sum/individuals in household; CRP - C-reactive protein; AH - arterial hypertension; ref. - reference; LVRT - left ventricular relative thickness; LVMI - left ventricular mass index.

alterations in their cardiac morphology and, thus, worse prognosis. The cardiovascular system of those patients should be more carefully and specifically considered to prevent that excessive mortality.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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