C - Reactive Protein Predicts All-Cause Mortality in Hemodialysis Patients

Gj. Selim, O. Stojceva –Taneva, R. Grozdanovski, A. Sikole, V. Amitov, S. Gelev, L. Trajceska
Department of Nephrology, Clinical Center, University "Sv. Kiril i Metodij" Skopje, Republic of Macedonia

Introduction

Mortality in dialysis patients remains extremely high despite significant improvements in the provision of dialysis over the past 20 years. It once was believed that factors related to dialysis treatment and technique were the main causes of poor clinical outcome, but a recent multicenter, randomized clinical trial known as the HEMO Study failed to show an improvement in mortality or hospitalization by increasing dialysis dose or using high-flux dialysis membranes[1]. The medical determinants of mortality in dialysis patients are well appreciated, but available evidence suggests that among potential candidates for the high rate of hospitalization and mortality in dialysis patients both malnutrition and inflammation continue to be at the top of the list. Epidemiological studies repeatedly and consistently have shown a strong association between clinical outcome and inflammation in dialysis patients [2, 3]. Our study objective was to evaluate the factors associated with all-cause mortality in a cohort of hemodialysis patients treated in a single hemodialysis center.

Methods

A total of 217 patients on hemodialysis (129 men, 88 women) were followed up for a period of 24 months (between January 2003 and December 2004). In 212 patients, dialysis was performed three times per week, in 5 patients two times per week. Bicarbonate solution was used as the dialysate in all patients. Serum albumin, CRP (C-reactive protein) and hemoglobin (Hg) were measured monthly, and serum fibrinogen every third month. Normal value for CRP was less than 6 mg/L.We also analyzed BMI (body mass index), predialysis blood pressure, PCR (protein catabolic rate), single pool-spKt/V and equilibrated -eKt/V. Single-pool spKt/V was calculated using a second –generation formula Daugirdas 2 and eKt/V was calculated using Daugirdas – Schneditz formula. *Statistical analysis*: Data from hemodialysis patients who died and from those alive after 24 months of follow-up were compared using t-test when normally distributed and rank-sum test when non-normally distributed. The risk of death among patients with varying quartiles of serum albumin (< 35, 35 to 40, and > 40 g/L), Hg (<100, 100 to 110, and > 110 g/L), fibrinogen (< 4, 4 to 5, and > 5 g/L) and CRP levels (<6; 6-10; 10-20; >20 mg/l) were compared using Kaplan-Meier survival function estimation. Multivariate analysis was performed using the Cox proportional hazards model to determine which factors are most closely associated with the risk for death.

Results

During the follow-up period of two years, fifty-five (25.3%) out of 217 patients died (31 men - 56.4%, 24 women - 43.6%), most from cardiovascular events - myocardial infarction, congestive heart failure, sudden death and stroke – 31 patients out of 55 pt, 56%. Noncardiac causes of death were septicemia (15 pt, 27%), neoplasma (4 pt, 7%) or other unknown causes (5 pt, 9%). The patients who died had significantly higher serum levels of CRP (34.26 ± 21.72 vs 8.74 ± 7.013, p=0.000), fibrinogen (5.28 ± 1.28 vs 4.42 ± 0.97, p=0.000), but lower serum levels of albumin (36.13 ± 4.32 vs 39.42 ± 4.36, p=0.000), Hg (93.72 ± 16.03 vs 108.83 ± 12.50, p=0.007), spKt/V (1.14 ± 0.25, vs 1.21 ± 0.19, p=0.049), eKt/V (1.00 ± 0.21, vs 1.10 ± 0.17 p=0.038) and were significantly older than those who survived (54.64 ± 12.75 vs 47.28 ± 15.25 p=0.001). The duration of dialysis treatment in hours was significantly shorter (3.95 ± 0.24 vs 4.04 ± 0.19 p=0.007) and ultrafiltration was significantly less (2.80 ± 0.69 vs 3.29 ± 0.91 p= 0.000) in patients who died during the follow-up period. However, duration on HD in years, predialysis blood pressure, BMI did not differ between the two groups.

The total group of patients showed a negative linear correlation between CRP and serum albumin levels (R= -0.365, p=0.0000), Hg (R= -0.444, p=0.0000), spKt/V (R= -0.211, p=0.0021), eKt/V (R= -0.210, p=0.0022), and positive linear correlation with age (R= 0.221, p=0.0013) and fibrinogen (R= 0.378, p=0.0000).

Kaplan-Meier survival estimates of patients from varying CRP quartiles (<6; 6-10; 10-20; >20 mg/l) differed among the four groups (log-rank test, p=0.00000). The group with the greatest CRP (>20 mg/l) had the lowest survival curve (Fig 1). Kaplan–Meier survival curves among the subgroups with varying albumin (< 35, 35 to 40, and > 40 g/L), Hg (<100, 100 to 110, and > 110 g/L), fibrinogen (< 4, 4 to 5, and > 5 g/L) levels, showed also statistically significant difference (p= 0.0008, p= 0.0395, and p= 0.0000) respectively.

Correspondence to: Gj. Selim, Department of Nephrology, Clinical Center, University "Sts. Cyril and Methodius", Skopje, Republic of Macedonia
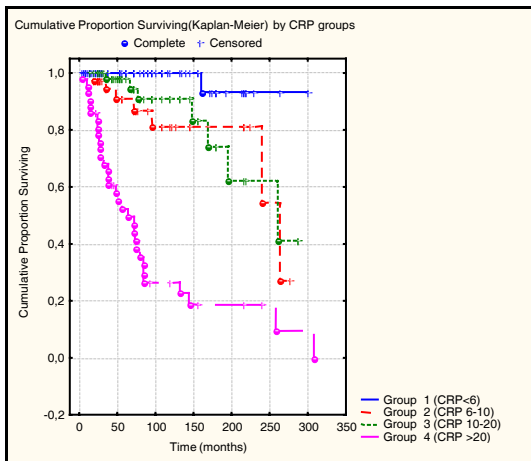
Fig 2. Kaplan – Meier estimate of
survival in hemodialysis patients
with serum C-reactive protein

Multivariate analysis using the Cox proportional hazards
model showed that only high CRP level, low Hg and older
age (chi-square=101.03, p=0.0000) were predictors for
death (Table 1).

Table 1. Parameters that predict all- cause mortality in the
Cox Proportional Hazards Model including C- Reactive
protein

Parameter	Beta	t-value	p
Age	0.0567	3.97592	**0.000070**
Hg	-0.0293	-2.97822	**0.002901**
Alb	-0.0406	-0.91508	0.360158
Fibrinogen	-0.2165	-1.25159	0.210727
CRP	0.0376	4.05006	**0.000051**

Chi-Square = 106.732, p=0.0000

Serum level of albumin did not show to be predictive. But,
when CRP was excluded from the Cox model, low serum
albumin level did show to be a predictor of death, followed
by older age and low Hg (chi-square=90.54, p=0.0000).
(Table 2)

Table 2. Parameters that predict all- cause mortality in the
Cox Proportional Hazards Model excluding C- Reactive
protein

Parameter	Beta	t-value	p
Age	0.0428	3.38184	**0.000721**
Hg	-0.0359	-3.88381	**0.000103**
Alb	-0.1025	-2.43354	**0.014958**
Fibrinogen	0.15497	1.15961	0.246216

Chi-Square = 90,5440 p=0.0000

Conclusions
Many investigators have observed that both malnutrition
and inflammation tend to occur concurrently and coexist in
dialysis patients and many factors that engender one of
these conditions also lead to the other.[2, 3] Inflammation is
major risk factor for mortality in dialysis patients, yet the

origin of chronic inflammation in this patients remains
unclear[4]. Numerous studies have shown that
hypoalbuminemia predicts death in hemodialysis patients.
These data suggest that serum albumin concentration
reflects the presence of acute – phase response and is not
primarily a marker of poor nutrition in dialysis patients[5].
Several studies have confirmed that inflammation, as
reflected by elevated levels of CRP is significant
independent predictor of mortality in dialysis patients.[6, 7, 8, 9]
In our study presented here, patients who died had
significantly lower serum levels of albumin, however, in
the multivariate Cox proportional hazards model albumen
lost its significance as risk factor for all-cause mortality,
because only high CRP level, low Hg, and older age were
predictors for death. However, if CRP was not taken into
account in the multivariate analysis, serum albumen
remained, after age and again low Hg, the strongest
predictor for all-cause mortality. In accordance with other
study [3], serum fibrinogen as one of the positive acute-
phase protein, in this study, in the multivariate Cox analysis
failed to be a predictor of mortality in dialysis patients.
It can be concluded that all-cause mortality in our study
group, although associated with low albumin, may not be
due to malnutrition per se, but rather to severe
inflammation, because CRP was a stronger predictor of
death than low albumin.

References:
1. Eknoyan G, Beck GJ, Cheung AK, et al: Effect of
   dialysis dose and membrane flux in maintenance
   hemodialysis. *N Eng J Med* 2002;347, 2010-2019
2. Qureshi AR, Alvestrand A, Divino-Filho JC, et al:
   Inflammation, malnutrition and cardiac disease as
   predictors of mortality in hemodialysis patients. *J Am
   Soc Nephrol* 2002;13:S28-S36
3. Zimmermann J, Herrlinger S, Pruy A, Metzger Th,
   Wanner C. Inflammation enhances cardiovascular risk
   and mortality in hemodialysis patients. Kidney
   International, 1999;Vol 55, 648-658
4. Kimmel PL, Phillips TM, Simmens SJ, et al:
   Immunologic function and survival in hemodialysis
   patients. *Kidney International*, 1998;Vol 54, 236-244
5. Qureshi AR, Alvestrand A, DAnielsson A, Divino-
   Filho JC, Gutierrez A, Lindholm B, Bergstrom J:
   Factors predicting malnutrition in hemodialysis
   patients: A cross-sectional study. *Kidney I*nt 1998;53:
   773-782
6. Jane Y.Yeun, Richard A. Levi, Viput MAnadilok, and
   George A. Kaysen: C-Reactive Protein predicts al-
   cause and cardiovascular mortality in hemodialysis
   patients. *Am J Kidney Dis* 2000;35:469-476
7. Christoph Wanner and Thomas Metzger: C-reactive
   protein a marker for all-cause and cardiovascular
   mortality in hemodialysis patients. *Nephrol Dial
   Transplant* 2002;(S 17);29-32
8. Tripepi G, Mallamaci F, Zoccali C: Inflammation
   markers, adhesion molecules and all-cause and
   cardiovascular mortality in patients with ESRD:
   searching for the best risk marker by multivariate
   modeling. *JAm Soc Nephrol* 2005;16 (S 1), S83-88

9.   Korevaar JC, van Manen JG, Dekkewr FW,   Waart DR, Boeschoten EW, Krediet RT: Effect of an increase in C-reactive protein level during a hemodialysis session on mortality. *J Am Soc Nephrol.* 2004;15 (11), 2916-2922