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ASSOCIATION BETWEEN HAEMOGLOBIN LEVEL AND ALL-CAUSE MORTALITY IN HAEMODIALYSIS PATIENTS: THE LINK WITH INFLAMMATION AND MALNUTRITION

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Abstract: Although anaemia management has improved in haemodialysis (HD) patients in recent years, many of them still have haemoglobin (Hb) levels below the current recommendations. The consequent anaemia could be one of the links between malnutrition and inflammation, and higher mortality in HD patients. The study objective was to determine the relationship between Hb levels and outcome in patients undergoing HD, accounting for inflammation and malnutrition.

We retrospectively analysed a total of 236 patients on HD between January 2003 and December 2005, classified by absence or presence of inflammation and malnutrition (defined as serum albumin levels < 40 g/L and CRP > 8mg/l). Serum levels of Hb, ferritin, creatinine, cholesterol, triglycerides, HDL (high-density lipoprotein cholesterol), LDL (low-density lipoprotein cholesterol), albumin and CRP were measured monthly, fibrinogen was measured every third month. Over the period of three years, 73 out of 236 patients (30%) had died, most from cardiovascular diseases (62%). Presence of inflammation and malnutrition (in 44% of patients) was associated with older age (60.69 ± 12.46 vs. 54.52 ± 12.37, p = 0.0002), lower levels of Hb (99.53 ± 14.97 vs. 111.86 ± 10.38 g/l, p = 0.0000), creatinine (835.88 ± 179.84 vs. 1069.98 ± 821.23 μmol/l, p = 0.0047), albumin (36.58 ± 3.41 vs. 40.32 ± 2.82 g/l, p = 0.0000), cholesterol (4.32 ± 1.04 vs. 4.75 ± 1.09 mmol/l, p = 0.0025) and higher levels of fibrinogen (4.94 ± 1.18 vs. 4.29 ± 0.91g/l, p = 0.0000) and CRP (30.42 ± 29.47 vs. 5.24 ± 4.89 mg/l, p =

0.0000). The Kaplan-Meier analysis showed that, irrespective of the absence or presence of inflammation and malnutrition, the all-cause mortality was higher in patients with Hb < 110 g/l (Log-Rank, p = 0.00147; p = 0.00222). On the other hand, Kaplan-Meier showed that, irrespective of the absence or presence of anaemia (Hb > 110 g/l and Hb < 110 g/l), the all-cause mortality was higher in patients with the presence of inflammation and malnutrition (Log-Rank, p = 0.00222; p = 0.00263). The Cox proportional hazard analysis, adjusting for age, showed that only lower serum levels of Hb and higher CRP were associated with all-cause mortality (chi-square = 110,306, p = 0.0000).

Our findings confirm the association of Hb levels < 110 g/L with higher mortality among maintenance HD patients, especially in patients with the presence of inflammation and malnutrition. Further investigation of the relationships among anaemia, inflammation and malnutrition and survival is warranted.

Key words: hemodialysis, anaemia, malnutrition and inflammation, all-cause mortality, CRP.

Introduction

Anaemia is a common complication of uraemia and associations between Hb levels and mortality and morbidity have been studied with conflicting results in ESRD patients [1, 2, 3, 4, 5]. Although anaemia management using the recombinant human erythropoietin (EPO) has improved in HD patients.over recent years, many of them still have haemoglobin Hb levels below the current recommendations [6, 7, 8].

Refractory anaemia appears to be more common in dialysis patients who also have inflammation and/or malnutrition [9]. It is not completely clear how inflamemation and malnutrition are related to dialysis–associated refracttory anaemia pathophysiologically [18]. Several previous studies have reported an association between anaemia and inflammation in dialysis patients, reflected in a high serum concentration of CRP [9, 10]. An inverse association between albumin and other more specific nutriational markers and the required EPO dose has also been reported. [11] The consequent anaemia could be one of the links between the malnutrition-inflammation-arteriosclerosis (MIA) syndrome and the higher rates of hospitalisation and mortality in HD patients [1]. However, the possible interactions between inflammatory and nutritional markers and their impact on refractory anaemia, as potentially modifiable risk factors for dialysis-associated morbidity and mortality, are still unclear [6].

The study objective was to determine the relationship between Hb levels and outcome in patients undergoing HD, accounting for inflammation and malnutrition.

Materials and Methods

Study population

We retrospectively followed up a total of 236 patients (143 men and 93 women) on HD between January 2003 and December 2005. An inclusion criterion was maintenance HD for at least 6 months. Dialysis was performed three times a week for 11.93 ± 0.75 hr/week (range from 9 to 13.35 hr/week). Causes of end-stage renal disease (ESRD) were chronic glomerulonephritis in 52 patients (22%), diabetes mellitus in 39 patients (16.5%), polycystic kidney disease in 17 patients (7%), nephroangiosclerosis in 40 patients (17%), interstitial nephritis in 40 patients (17%), plasmocytoma in 3 patients (1.3%), Balkan nephropathy in 2 patients (0.85%) and other or unknown cause in 43 patients (18%).

Haemodialysis treatment was performed using conventional bicarbonate – buffered dialysate in all patients The average spKt/V in these patients was 1.21 ± 0.20 (0.66–1.75) and PCR (g/kg/d) was 1.04 ± 0.15 (0.58–1.46). The patients were on treatment with recombinant human erythropoietin (EPO), according to the the recommendations of the European Best Practice Guidelines (EBPG) on anaemia management in patients with chronic renal failure. The main demographic and clinical characteristics of the patients included in the study are detailed in Table 1.

Table 1 – Табела 1
Clinical and biochemical parameters of the study population
Клинички и лабораториски параметри на испитуваната популација

Age (year)	57.18 ± 12.89
Duration of HD treatment (months)	93.80 ± 70.45
Smokers	
Former	109 (47%)
Current (n; %)	83 (35%)
Systolic BP (mmHg)	136.29 ± 22.65
BMI (kg/m^2)	23.94 ± 4.27
Haemoglobin (g/L)	106.38 ± 13.98
Ferritin (μg/l)	626.76 ± 331.51
Creatinine (μmol/l)	932.09 ± 215.11
Albumin (g/L)	38.66 ± 3.60
Fibrinogen (g/L)	4.55 ± 1.07
Cholesterol (mmol/l)	4.56 ± 1.08
HDL cholesterol (mmol/l)	0.99 ± 0.27
LDL cholesterol (mmol/l)	2.64 ± 0.88
C-reactive protein (mg/l)	16.31 ± 23.40

Laboratory Measurements

Serum levels of Hb, ferritin, creatinine, cholesterol, triglyceride, HDL (high-density lipoprotein cholesterol), LDL (low-density lipoprotein cholesterol) and albumin were measured monthly, using standard methods, at the Institute of biochemistry, Ss. Cyril and Methodius University, Skopje. Serum concentration of CRP was measured monthly, by a nephelometric immunoassay, and fibrinogen was measured every third month, by the thrombin time method in a blood sample anticoagulated with sodium citrate. Single-pool spKt/V was calculated monthly, using a second-generation formula Daugirdas 2 and PCR (protein catabolic rate) was calculated using the formula with interdialytic rise in blood urea.

To better distinguish individuals with any evidence of inflammation and malnutrition, a composite variable combining serum albumin and CRP levels was used to categorise the study population into 2 subgroups: presence or absence of inflammation and malnutrition. The presence of inflammation and malnutrition was defined as achievement of a priori cutoffs for 2 variables from the study population. The cutoff level for serum albumin was less than 40 g/L and for CRP, 8 mg/l or higher.

Statistical analysis

Data are presented as mean ± SD or median and range, as appropriate, with P less than 0.05 indicating statistical significance. Comparison between 2 groups for normally distributed variables was performed by using Student t-test. Correlations were performed by using Spearman rank test. The Kaplan-Meier test was used for analysis of survival. The data were censored at the time of death. Differences in survival were assessed with the log rank test. Multivariate Cox proportional hazards analysis to adjust for patient characteristics, was performed to determine the factors that were most closely associated with the all-cause mortality. All data analyses were performed with Statistica 6 for Windows.

Results

Patient Characteristics

The mean age of the patients was 57.18 ± 12.89 years (men 56.44 ± 12.58, women 58.31 ± 13.39) and duration of haemodialysis treatment in months was 93.80 ± 70.45, ranging from 6 to 311 months (men 89.96 ± 69.66, women 101.39 ± 72.59). During the follow-up period of three years, 73 out of 236 patients (30.1%) died (58.9% men n = 43; 41.1% women n = 30) mostly from

cardiovascular diseases (CVD) (45 out of 73; 61.6%) and according to the HEMO Study Death Classification (12), the causes of death from CVD were ischaemic heart disease (n = 11), congestive heart failure (n = 15), arrhythmias and conduction problems (n = 5), cerebrovascular disease (n = 11) and peripheral vascular disease (n = 3). Noncardiac causes of death were infection/sepsis (n = 17), neoplasms (n = 4) or other unknown causes (n = 7).

The patients who died were significantly older than those alive at 36 months, 61.15 ± 11.59 vs. 54.95 ± 12.89, p = 0.0000, had significantly lower serum levels of Hb, 95.99 ± 15.39 vs. 110.90 ± 10.59, p = 0.0000, lower serum levels of albumin 36.49 ± 3.89 vs. 39.60 ± 3.04, p = 0.0000, and they had significantly higher serum levels of CRP, 35.56 ± 34.15 vs. 8.16 ± 8.39, p = 0.0000. spKt/V and serum levels of creatinine were significantly lower (1.15 ± 0.22 vs.1.23 ± 0.19, p = 0.004; 794.82 ± 184.82 vs. 991.88 ± 200.55, p = 0.000), but the serum level of fibrinogen was significantly higher (5.10 ± 1.19 vs. 4.39 ± 0.98, p = 0.000) in the patients who died. There was no difference in mean levels of cholesterol, triglycerides, HDL and LDL between the patients who died and those alive at 36 months.

Relationships between haemoglobin, albumin and CRP

As shown in Table 2, both Hb and albumin levels were negatively correlated with CRP (r = -0.48, p = 0.000 and r = -0.39, p = 0.000, respectively). In this subset of 236 patients, there remains a positive linear correlation between Hb and serum albumin levels (r = 0.35, p = 0.0000).

Table 2 – Табела 2

Correlation matrix of CRP, Albumin and Haemoglobin[a]

Корелациони матрикс меѓу CRP, албумин и хемоглобин

	Age	***Kt/V***	***Cr***	***Alb***	***Hb***	***Hol***	***Fib***	***CRP***
Hb	-0.17 (0.00)	0.24 (0.00)	0.35 (0.00)	0.35 (0.00)	–	0.14 (0.03)	-0.24 (0.00)	-0.48 (0.00)
Alb	-0.31 (0.00)	n.s.	0.52 (0.00	–	0.35 (0.00)	0.29 (0.00)	-0.20 (0.00)	-0.39 (0.00)
CRP	0.23 (0.00)	-0.20 (0.00)	-0.31 (0.00)	-0.39 (0.00)	-0.48 (0.00)	n.s.	0.41 0.00)	–

[a] Data are Spearman rank correlation coefficients and p values.

Comparison between haemoglobin levels and inflammatory/nutrition status

In this study population, Hb levels > 110 g/l were achieved in 45% of patients (no = 106). As shown in Table 3, patients with Hb levels > 110 g/l were significantly younger with a longer duration of HD in months. They had higher levels of albumen and creatinin, but lower levels of fibrinogen and CRP.

Table 3 – Табела 3

Variables significantly different between the groups according to haemoglobin level (below or above 110 g/l)

Сигнификантно значајни разлики во однос на хемоглобински вредности над и под 110 г/л

Characteristics	**Haemoglobin < 110 g/L (n = 128)**	**Haemoglobin > 110 g/L (n = 106)**	**P**
Age	59.04 ± 11.94	55.12 ± 13.43	0.0191
Duration of HD (mo)	80.48 ± 66.19	112.54 ± 72.78	0.0005
Systolic BP (mmHg)	141.37 ± 22.92	138.16 ± 20.94	0.0000
spKt/V	1.18 ± 0.20	1.24 ± 0.19	0.0200
Haemoglobin (g/L)	97.03 ± 11.47	117.67 ± 6.44	0.0000
Creatinine	879.68 ± 191.48	995.37 ± 226.67	0.0000
Albumin (g/L)	37.89 ± 4.05	39.58 ± 2.73	0.0003
Fibrinogen (g/L)	4.76 ± 1.15	4.34 ± 0.94	0.0040
C-reactive protein (mg/l)	22.18 ± 23.45	9.34 ± 21.57	0.0000

Overall, 44 % (n = 104) of the dialysis patients had evidence of inflammation and malnutrition. The presence of inflammation and malnutrition was associated with older age, lower levels of Hb, creatinine, albumen, triglycerides, cholesterol, HDL cholesterol, and LDL cholesterol and higher levels of fibrinogen and CRP (Table 4).

Survival analysis

In this study population the cumulative survival was markedly dependent on Hb levels and presence or absence of inflammation and malnutrition. Patients with Hb < 110 g/l and presence of inflammation and malnutrition had a higher mortality rate than those with Hb > 110 g/l (Log-Rank, p = 0.00000) and absence of inflammation and malnutrition, (log-rank, p = 0.00000) (curves not shown).

Table 4 – Табела 4

Comparison between the two subgroups of study population based on inflammatory and nutrition status
Споредба на двете групи во зависност од присуство или отсуство на инфламација и малнутриција

Characteristics	Presence of Inflammation/Malnutrition (n = 104)	Absence of Inflammation/Malnutrition (n = 130)	p
Age	60.69 ± 12.46	54.52 ± 12.37	**0.0002**
Duration of HD (mo)	90.08 ± 74.79	98.06 ± 67.39	0.3932
BMI (kg/m^2)	24.21 ± 4.69	23.72 ± 3.93	0.3867
spKt/V	1.18 ± 0.22	1.23 ± 0.18	0.0712
PCR (g/kg/d)	1.03 ± 0.17	1.06 ± 0.13	0.1591
Haemoglobin (g/L)	99.53 ± 14.97	111.86 ± 10.38	**0.0000**
Ferritin (μg/l)	627.05 ± 393.64	626.54 ± 277.72	0.9908
Creatinine	835.88 ± 179.84	1069.98 ± 821.23	0.0047
Lipid levels (mmol/l)	7.51 ± 1.62	8.24 ± 1.89	**0.0021**
Triglicerid (mmol/l)	1.88 ± 0.90	2.23 ± 1.26	**0.0191**
Cholesterol (mmol/l)	4.32 ± 1.04	4.75 ± 1.09	**0.0025**
HDL cholesterol (mmol/l)	0.94 ± 0.26	1.03 ± 0.27	**0.0079**
LDL cholesterol (mmol/l)	2.50 ± 0.79	2.74 ± 0.94	**0.0079**
Albumin (g/L)	36.58 ± 3.41	40.32 ± 2.82	**0.0000**
Fibrinogen (g/L)	4.94 ± 1.18	4.29 ± 0.91	**0.0000**
C-reactive protein (mg/l)	30.42 ± 29.47	5.24 ± 4.89	**0.0000**

Survival of patients using Kaplan-Meier analysis was estimated in two groups, separately, of the study population, according to the presence or absence of inflammation-malnutrition. The results showed that irrespective. of the presence or absence of inflammation-malnutrition, all-cause mortality was higher in patients with Hb < 110 g/l (log-rank, p = 0.00147; p = 0.00222) (Figure 1 and 2).

Then the study population was divided into two groups according to their Hb level. Kaplan-Meier analysis showed that irrespective of the level of Hb, all-cause mortality was higher in patients where inflammation-malnutrition was present. (log-rank, p = 0.00222; p = 0.00263) (Figure 3 and 4) (Table 5).

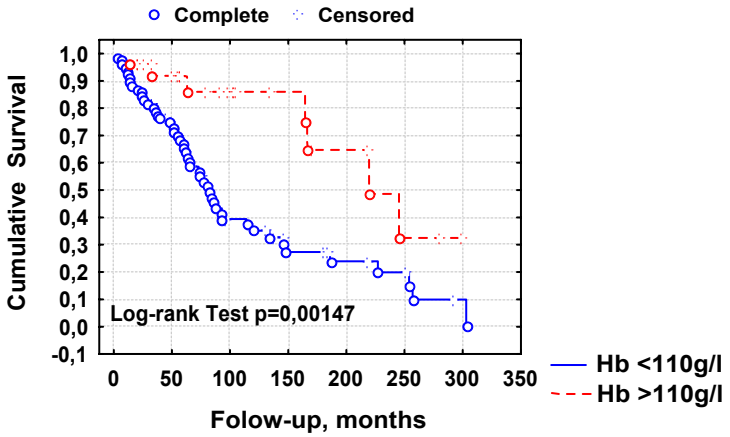

Figure 1 – Comparison of survival (Kaplan-Meier) according to Hb level in the group with inflammation-malnutrition
Слика 1 – Kaplan-Meier криви на преживување при присуство на инфламација-малнутрициja во однос на Хб вредности

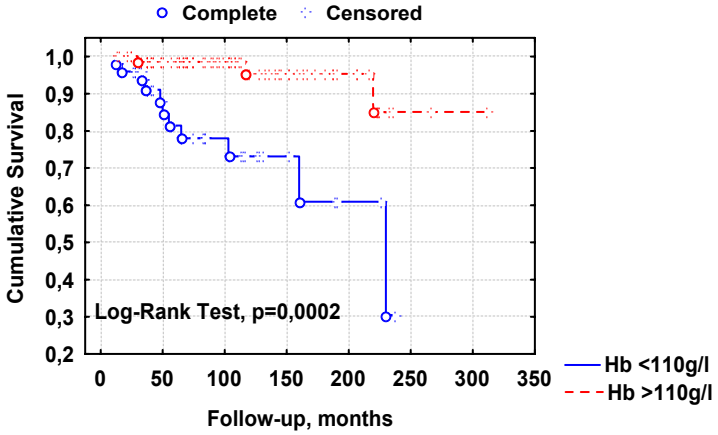

Figure 2 – Comparison of survival (Kaplan-Meier) according to Hb level in the group without inflammation-malnutrition
Слика 2 – Kaplan-Meier криви на преживување при отсуство на инфламација-малнутрициja во однос на Хб вредности

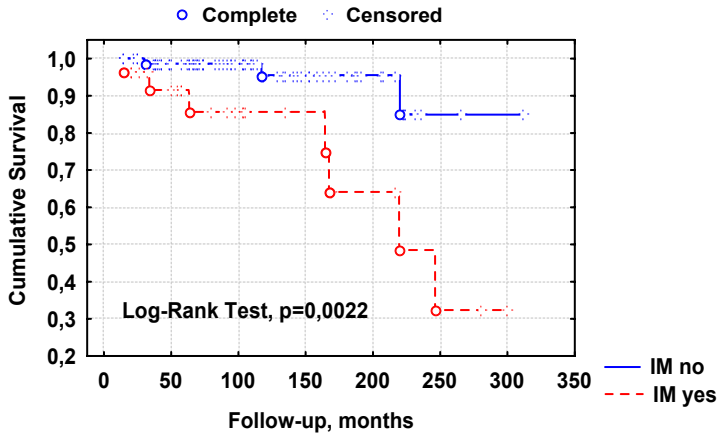

Figure 3 – Comparison of survival (Kaplan-Meier) according to presence or absence of inflammation-malnutrition in the non-anaemic group
Слика 3 – Kaplan-Meier криви на преживување во група со Хб > 110 г/л, во однос на инфламација и малнутриција

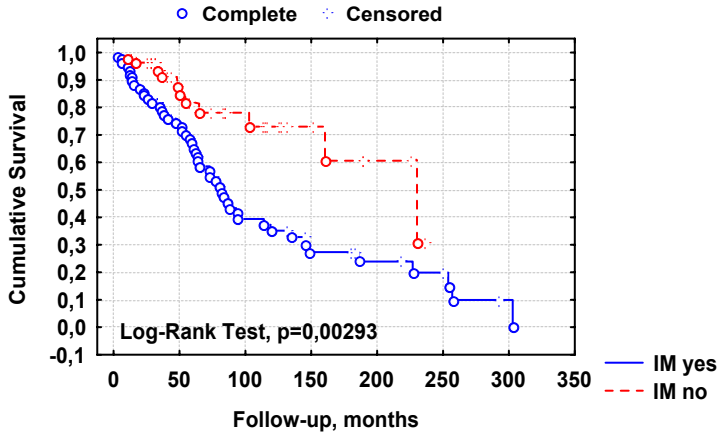

Figure 4 – Comparison of survival (Kaplan-Meier) according to presence or absence of inflammation-malnutrition in the anaemic group
Слика 4 – Kaplan-Meier криви на преживување во група со Хб < 110 г/л, во однос на инфламација и малнутриција

Table 5 – Табела 5

Parameters that predict all- cause mortality in the Cox Proportional Hazards Model after a follow-up period of 36 months

Параметри кои предвидуваат вкурен морталитет врз база на Cox Proportional Hazards Model по период на следење од 36 месеци

Table 5. Parameters that predict all-cause mortality in the Cox Proportional Hazards Model after a follow-up period of 36 months

Paramt	Beta	t	p
Age	0.028	2.723	**0.006**
Hb	-0.053	-5.635	**0.000**
Alumin	-0.0189	-0.462	0.644
CRP	0.0229	6.688	**0.000**

Chi-Square = 110.306, p = 0.0000

The Cox proportional hazards model demonstrated that only Hb and CRP levels were predictive of all-cause mortality in HD patients (Table 4)

Discussion

Anaemia is a common complication of uremia and a major contributor to morbidity and mortality in HD patients. Over the last 15 years, the availabity of recombinant human EPO has led to the almost complete disappearance of severe anaemia in HD patients; however, despite an increase in its use and average dose, a substantial percentage of patients still fail to achieve the Hb targets recommended by the international guidelines. [6, 7, 8] The European Survey on Anaemia Management 2003 (ESAM), for example, showed that 33.9% of the patients on dialysis did not reach the recommended target Hb level > 11 g/dl and 13.2 % even had a Hb level < 10 g/dl. (13). Dialysis Outcomes and Practice Patterns Study (DOPPS) also demonstrated that 55 % of HD patients in 1998-1999 and 49 % in the year 2000 had a Hb concentration below the EBPG recommendation [1]. The European guidelines recommend that at least 85% of haemodialysis patients should attain a Hb concentration of ≥ 11 g/dl. In the present investigation, Hb levels > 110 g/l were achieved in 45% of patients and

55% of our HD patients had a Hb concentration below the minimum recommended level of 11 g/dl.

A correlation between survival and Hb concentration has been established in large retrospective studies and in a prospective cohort study [2, 3, 4]. The concerning results about target haemoglobin levels in HD patients on mortality developed from clinical trials and observational studies have given conflicting results [5]. The normal haematocrit trial of Besarab *et al.,* showed no benefit, and a possible risk, of correcting the haematocrit from 30% to 42% in haemodialysis patients with NYHA class I to III cardiac disease [4]. In a large prospective, observational study of HD patients in five European countries, the risk of mortality in these patients was 5% lower for each 1g/dl higher Hb concentration [1]. A recent meta-analysis of randomized controlled trials emphasizes that Hb values < 12 g/dl are associated with a lower all-cause mortality than values >13 g/dl, whereas values < 10 g/dl are associated with increased risk of seizures. Therefore, in CKD patients with CVD, the benefits associated with higher Hb targets (reduced seizures) are outweighed by potential harmful effects (increased risk of hypertension and death). It was concluded that the preferred target Hb should be < 12 g/dl. [3]. In this study we found that patients who died had significantly lower serum levels of Hb (~96 g/l) than those alive at 36 months (~111 g/l). We also found that the group of patients with Hb > 110 g/l had a longer duration of HD in months than those with Hb levels < 110 g/l (112 months vs. 80 months). The Kaplan-Meier curve showed that patients with Hb levels < 110 g/l had a higher mortality rate than those with Hb levels > 110 g/l (Log-Rank, p = 0.00000).

Several previous studies have reported an association between anaemia and inflammation in dialysis patients, reflected by a high serum concentration of CRP [9, 10] or such proinflammatory cytokines as IL-6 and TNF-α. [14, 15]. A large proportion of HD patients also have protein energy malnutrition, low serum levels of albumin and other specific nutritional markers which are predictors of the response of EPO [11]. In our study the presence of inflammation and malnutrition was defined as achievement of *a priori* cutoffs for 2 variables from the study population (for serum albumin levels, the cutoff value was less than 40 g/L and for CRP, 8 mg/l or higher). Wanner *et al*. [16] demonstrated that a value of CRP > 8 mg/l is a good indicator of cardiovascular and global mortality in a group of HD patients who were followed-up over 4 years. In our study, too, the patients alive at 36 months had CRP levels of 8 mg/l. We believe that the cut-off point for the serum level of CRP > 8 mg/l recommended by the EDTA guidelines [17] is a reliable marker of inflammation in HD patients and this is also confirmed in the study of Waner who showed that the relationship between CRP and mortality in HD patients appeared in cases of elevated inflammation. About 35% to 65% of HD patients show signs of inflammation that could be a cause of anaemia through the suppression of bone marrow erythropoiesis by a number of cytokines [19]. Overall, 44% of the HD patients in our

study had evidence of inflammation and malnutrition. Presence of inflammation and malnutrition was associated with older age, lower Hb, creatinine, albumen, triglycerides, cholesterol, HDL cholesterol, LDL cholesterol and higher levels of fibrinogen and CRP. Serum ferritin levels were not different between the groups. Based on our study results, it appears that interactions between anaemia and inflammation-malnutrition are very complex and difficult to elucidate, because the results of the survival analysis show a high correlation of all-cause mortality and presence of inflammation-malnutrition, irrespective of anaemia, as well as a high correlation of all-cause mortality and anaemia, irrespective of inflammation- malnutrition. We must emphasize, however, that the role of inflammation in our study group is more important than malnutrition (probably a result of the chronic inflammatory state), because the Cox proportional hazards model showed that only low Hb and high CRP and not albumen were predictive for all-cause mortality. The results of this study suggest that the link between elevated levels of CRP as a marker of inflammation and mortality in HD patients may be the presence of anaemia. The survival of HD patients may be improved by applying the recommendations for the management of inflamemation-induced anemia.

Conclusion

Our findings confirm the association of Hb levels < 110 g/L with higher mortality among maintenance HD patients, especially in patients with a presence of inflammation and malnutrition. Further investigation of the relationships among anaemia, inflammation and malnutrition and survival is warranted.

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Резиме

АСОЦИРАНОСТ НА ХЕМОГЛОБИН СО ВКУПНИОТ МОРТАЛИТЕТ КАЈ ПАЦИЕНТИТЕ НА ХЕМОДИЈАЛИЗА: ПОВРЗАНОСТА СО ИНФЛАМАЦИЈА И МАЛНУТРИЦИЈА

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Последните години, покрај подобрениот третман на реналната анемија, дел од пациентите на хемодијализа (ХД), остануваат со хемоглобински (Хб) вредности кои се под нивото на препорачаните таргети. Последователната анемија, преку поврзаноста со инфламацијата и малнутрицијата, е една од причините за поголем морталитет кај пациентите на ХД. Целта на студијата е процена на релацијата на вредностите на Хб со исходот на пациентите на ХД, пред с# во услови на инфламација и малнутриција.

Ретроспективно беа следени вкупно 236 пациенти на ХД (во период од јануари 2003-та до декември 2005-та година), поделени во две групи, во зависност од присуство или отсуство на инфламација и малнутриција (дефинирано преку ЦРП > 8 mg/l и албумен < 40 g/l). Серумските вредности за Хб, феритин, креатинин, холестерол, триглицериди, HDL (high-density lipoprotein cholesterol), LDL (low-density lipoprotein cholesterol), албумен и ЦРП беа анализирани месечно, додека фибриноген беше земен на три месеци. Во текот на тригодишното следење, починаа 73 пациенти од вкупно 236 (30%), при што најчеста причина за смрт беа кардиоваскуларните болести со 62%. Присуството на инфламација и малнутриција (кај 44% од пациентите) беше асоцирано со постара возраст (60,69 ± 12,46 н.с. 54,52 ± 12,37, p = 0,0002), пониски вредности за Хб (99,53 ± 14,97 н.с. 111,86 ± 10,38 g/l, p = 0,0000), креатинин (835,88 ± 179,84 н.с. 1069,98 ± 821,23 μmol/l, p = 0,0047), албумин (36,58 ± 3,41 н.с. 40,32 ± 2,82 g/l, p = 0,0000), холестерол (4,32 ± 1,04 н.с. 4,75 ± 1,09 mmol/l, p = 0,0025) и повисоки вредности за фибриноген (4,94 ± 1,18 н.с. 4,29 ± 0,91 g/l, p = 0,0000) и ЦРП (30,42 ± 29,47 н.с. 5,24 ± 4,89 mg/l, p = 0,0000). Kaplan-Meier'ова анализа покажа дека и во присуство, но и во отсуство на инфламација и малнутриција, вкупниот морталитет е повисок кај пациентите со Хб < 110 g/l (Log-Rank, p = 0,00147; p = 0,00222). Но, исто така, Kaplan-Meier'овата анализа покажа, дека и при Хб > 110 g/l, но и при Хб < 110 g/l, вкупниот морталитет е повисок кај пациенти со присуство на инфламација и малнутриција (Log-Rank, p = 0,00222; p = 0,00263). Во Cox'овиот модел, коригирана за возраст,

само ниските вредности на Хб и високите вредности на ЦРП, а не албуменот, беа асоцирани со вкупниот морталитет (chi-square = 110,306, p = 0,0000).

Нашите резултати ја потврдуваат асоцијацијата на анемијата со повисокиот морталитет кај пациентите на ХД, пред с# во услови на присутна инфламација и малнутриција. Идните истражувања треба да ја разјаснат релацијата на анемијата, инфламацијата и малнутрицијата, со преживувањето кај пациентите на ХД.

Клучни зборови: хемодијализа, анемија, малнутрицијa и инфламација, вкупен-морталитет, ЦРП.

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Table 1. Clinical and biochemical parameters of the study population
Табела 1. Клинички и лабараториски параметри на испитуваната популација

Age (year)	57.18 ± 12.89
Duration of HD treatment (months)	93.80 ± 70.45
Smokers	
Former	109 (47%)
Current (n; %)	83 (35%)
Systolic BP (mmHg)	136.29 ± 22.65
BMI (kg/m^2)	23.94 ± 4.27
Haemoglobin (g/L)	106.38 ± 13.98
Ferritin (μg/l)	626.76 ± 331.51
Creatinine (μmol/l)	932.09 ± 215.11
Albumin (g/L)	38.66 ± 3.60
Fibrinogen (g/L)	4.55 ± 1.07
Cholesterol (mmol/l)	4.56 ± 1.08
HDL cholesterol (mmol/l)	0.99 ± 0.27
LDL cholesterol (mmol/l)	2.64 ± 0.88
C-reactive protein (mg/l)	16.31 ± 23.40

Table 2. Correlation matrix of CRP, Albumin and Haemoglobin [a]
Табела 2. Корелациони матрикс меѓу CRP, албумин и хемоглобин

	Age	***Kt/V***	***Cr***	***Alb***	***Hb***	***Hol***	***Fib***	***CRP***
Hb	-0.17 (0.00)	0.24 (0.00)	0.35 (0.00)	0.35 (0.00)	-	0.14 (0.03)	-0.24 (0.00)	-0.48 (0.00)
Alb	-0.31 (0.00)	n.s.	0.52 (0.00	-	0.35 (0.00)	0.29 (0.00)	-0.20 (0.00)	-0.39 (0.00)
CRP	0.23 (0.00)	-0.20 (0.00)	-0.31 (0.00)	-0.39 (0.00)	-0.48 (0.00)	n.s	0.41 0.00)	-

[a] Data are Spearman rank correlation coefficients and p values

Table 3. Variables significantly different between the groups according to haemoglobin level (below or above 110 g/l)
Табела 3. Сигнификантно значајни разлики во однос на хемоглобински вредности над и под 110 г/л

Characteristics	**Haemoglobin < 110 g/L (n = 128)**	**Haemoglobin > 110 g/L (n = 106)**	
Age	59.04 ± 11.94	55.12 ± 13.43	0.0191
Duration of HD (mo)	80.48 ± 66.19	112.54 ± 72.78	0.0005
Systolic BP (mmHg)	141.37 ± 22.92	138.16 ± 20.94	0.0000
spKt/V	1.18 ± 0.20	1.24 ± 0.19	0.0200
Haemoglobin (g/L)	97.03 ± 11.47	117.67 ± 6.44	0.0000
Creatinine	879.68 ± 191.48	995.37 ± 226.67	0.0000
Albumin (g/L)	37.89 ± 4.05	39.58 ± 2.73	0.0003
Fibrinogen (g/L)	4.76 ± 1.15	4.34 ± 0.94	0.0040
C-reactive protein (mg/l)	22.18 ± 23.45	9.34 ± 21.57	0.0000

Table 4. Comparison between the two subgroups of study population based on inflammatory and nutrition status
Табела 4. Споредба на двете групи во зависност од присуство или отсуство на инфламација и малнутриција

Characteristics	Presence of Inflammation/Malnutrition (n = 104)	Absence of Inflammation/Malnutrition (n = 130)	p
Age	60.69 ± 12.46	54.52 ± 12.37	**0.0002**
Duration of HD (mo)	90.08 ± 74.79	98.06 ± 67.39	0.3932
BMI (kg/m^2)	24.21 ± 4.69	23.72 ± 3.93	0.3867
spKt/V	1.18 ± 0.22	1.23 ± 0.18	0.0712
PCR (g/kg/d)	1.03 ± 0.17	1.06 ± 0.13	0.1591
Haemoglobin (g/L)	99.53 ± 14.97	111.86 ± 10.38	**0.0000**
Ferritin (μg/l)	627.05 ± 393.64	626.54 ± 277.72	0.9908
Creatinine	835.88 ± 179.84	1069.98 ± 821.23	0.0047
Lipid levels (mmol/l)	7.51 ± 1.62	8.24 ± 1.89	**0.0021**
Triglicerid (mmol/l)	1.88 ± 0.90	2.23 ± 1.26	**0.0191**
Cholesterol (mmol/l)	4.32 ± 1.04	4.75 ± 1.09	**0.0025**
HDL cholesterol (mmol/l)	0.94 ± 0.26	1.03 ± 0.27	**0.0079**
LDL cholesterol (mmol/l)	2.50 ± 0.79	2.74 ± 0.94	**0.0079**
Albumin (g/L)	36.58 ± 3.41	40.32 ± 2.82	**0.0000**
Fibrinogen (g/L)	4.94 ± 1.18	4.29 ± 0.91	**0.0000**
C-reactive protein (mg/l)	30.42 ± 29.47	5.24 ± 4.89	**0.0000**

Table 5. Parameters that predict all- cause mortality in the Cox Proportional Hazards Model after a follow-up period of 36 months
Табела 5. Параметри кои предвидуваат вкупен морталитет врз база на Cox Proportional Hazards Model после период на следење од 36 месеци.

Table 5. Parameters that predict all-cause mortality in the Cox Proportional Hazards Model after a follow-up period of 36 months

Paramt	Beta	t	p
Age	0.028	2.723	**0.006**
Hb	-0.053	-5.635	**0.000**
Alumin	-0.0189	-0.462	0.644
CRP	0.0229	6.688	**0.000**

Chi-Square = 110.306, p=0.0000

The Cox proportional hazards model demonstrated that only Hb and CRP levels were predictive of all-cause mortality in HD patients (Table 4)

Figure 1. Comparison of survival (Kaplan-Meier) according to Hb level in the group with inflammation-malnutrition
Слика 1. Kaplan-Meier криви на преживување при присуство на инфламација-малнутриција во однос на Хб вредности

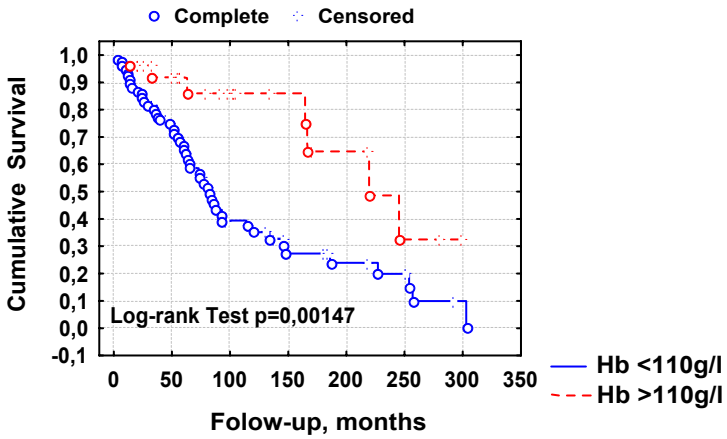

Figure 2. Comparison of survival (Kaplan-Meier) according to Hb level in the group without inflammation-malnutrition
Слика 2. Kaplan-Meier криви на преживување при отсуство на инфламација-малнутриција во однос на Хб вредности

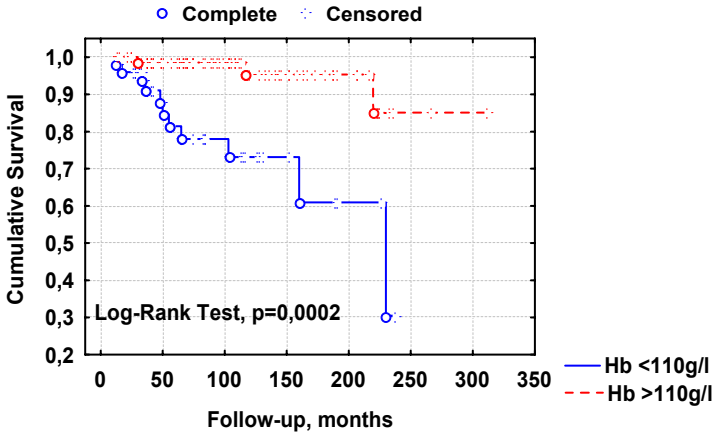

Figure3. Comparison of survival (Kaplan-Meier) according to presence or absence of inflammation-malnutrition in the non-anaemic group
Слика 3. Kaplan-Meier криви на преживување во група со Хб>110г/л, во однос на инфламација и малнутриција

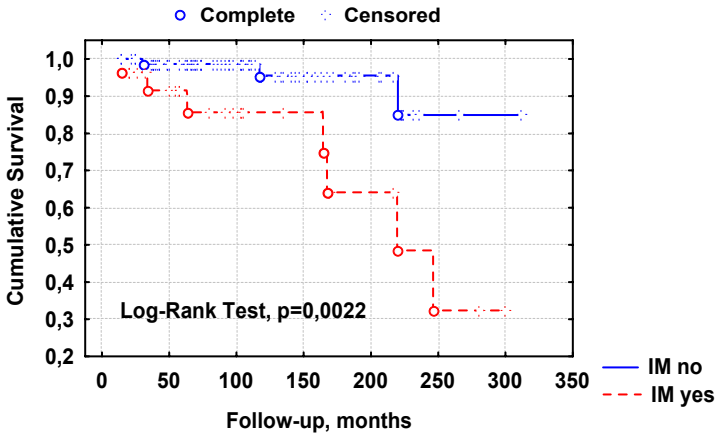

Figure 4. Comparison of survival (Kaplan-Meier) according to presence or absence of inflammation-malnutrition in the anaemic group

Слика 4. Kaplan-Meier криви на преживување во група со Хб<110г/л, во однос на инфламација и малнутриција