

THE ASSOCIATION OF LOW TRIIODOTHYRONINE SYNDROME, PROTEIN-ENERGY WASTING AND CHRONIC INFLAMMATION WITH MORTALITY IN PREVALENT DIALYSIS PATIENTS

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SUMMARY – This prospective study in prevalent dialysis patients investigated prognostic properties of low triiodothyronine syndrome, protein-energy wasting and chronic inflammation. Ninety-four prevalent dialysis patients were followed-up for a median of 39 months. Demographic, anthropometric and biochemical parameters were collected at baseline. Univariate and multivariate analysis was done using Cox regression analysis. ROC curve analysis using survival status as a classification variable was performed with the goal of determining optimal cut-off values for numerical variables. In our population, low total triiodothyronine (hazard ratio (HR) 2.19, $p=0.038$), catheter as vascular access (HR 2.76, $p=0.023$), higher vintage (HR 1.01, $p=0.014$) and higher Charlson comorbidity index (HR 1.28, $p=0.017$) were statistically significantly associated with inferior survival. In our group of steady-state dialysis patients, total triiodothyronine seemed to be the strongest predictor of inferior survival among thyroid hormones. Taking this parameter into account, it was possible to identify patients at an increased risk of death even after adjustment for other prognostically relevant variables. However, after further adjustment for significant risk factors, the impact of C-reactive protein and albumin on survival disappeared due to the overlapping prognostic properties. We concluded that triiodothyronine was an independent prognostic factor in our study group.

Key words: *Dialysis; Euthyroid sick syndrome; Inflammation; Risk factors; Croatia*

Introduction

Patients with end-stage renal disease (ESRD) are known to have a higher risk of mortality and morbidity than the general population. Risk factors for mortality in this group of patients are unique since there is a high prevalence of elderly patients with multiple comorbidities. Also, they have survived long enough to

develop kidney failure. There is the need to develop a special predictive model that could be applied to ESRD patients. Research has been focused on biomarkers that could be novel risk factors that increase the accuracy of prognosis in patients with ESRD¹.

One of the studied mortality risk markers in patients with ESRD is triiodothyronine (T3), whether in its free (fT3) or bound form (T3). Reduction of T3 levels, while the levels of thyroid-stimulating hormone (TSH) remain in the reference range, is known as the low T3 syndrome. It is the most frequently observed thyroid hormone alteration in ESRD patients²⁻⁴. Chronic kidney disease affects both the hypothalamus-pituitary-thyroid axis and thyroid hormone pe-

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Received January 11, 2018, accepted March 6, 2018

ripheral metabolism. Reduction in T3 concentrations has been linked to a decrease in peripheral synthesis of T3 from thyroxine (T4)². It has been shown in many survival studies so far that low T3 syndrome is a risk factor for mortality both in hemodialysis (HD)⁵⁻⁹ and peritoneal dialysis (PD) patients^{10,11}.

Another novel mortality biomarkers in ESRD patients are protein-energy wasting (PEW) and chronic inflammation¹. PEW is a state of decreased body stores of protein and fat masses. It can result from inadequate diet. However, in kidney disease there are some specific causes such as inflammatory processes, intercurrent catabolic illnesses, nutrient losses into dialysate, metabolic acidosis, resistance to insulin, growth hormone, and insulin-like growth factor-1, hyperglucagonemia, hyperparathyroidism, and loss of blood into the hemodialyzer, into stool or by blood drawing¹². Studies in well-characterized hemodialysis populations indicate that C-reactive protein (CRP) levels (as a marker of chronic inflammation) are a consistent predictor of survival¹, whereas serum albumin is known as a negative acute phase reactant, but also as one of the markers of PEW¹³.

In complex processes of acute and chronic inflammation in patients with ESRD, studies have shown strong association between inflammation markers and low T3 syndrome, where fT3/T3 was proven to be a significant and independent predictor of survival¹⁴⁻¹⁶. On the other hand, Ozen *et al.* showed in a large cohort of prevalent hemodialysis patients that fT3 was a strong predictor of mortality in crude and adjusted Cox models including albumin or high-sensitivity CRP (hsCRP); however, after further adjustment for both albumin and hsCRP, the impact of fT3 on mortality disappeared¹⁷. Another study performed by Fernández-Reyes *et al.* showed that low fT3 levels were not predictive of long-term mortality in a subgroup of stable HD patients, who could survive for more than 12 months¹⁸.

Our study aimed to investigate the steady-state correlation of thyroid hormones, CRP and serum albumin (and other surrogates of PEW) with mortality in our group of dialysis patients. Furthermore, taking into account a complex mortality risk factor profile of dialysis patients¹⁹, we studied correlations of available known risk factors with mortality in our patients, alongside low T3 syndrome, PEW and chronic inflammation.

Patients and Methods

Patients

In this observational prospective cohort study, prevalent HD and PD patients treated at Sestre milosrdnice University Hospital Centre in Zagreb and Dr Tomislav Bardek General Hospital in Koprivnica, were enrolled. Baseline demographic, anthropometric and biochemical parameters were collected from April to December 2014. September 20, 2017 was considered as the end of the study. Survival was determined from the day of enrolment, with a median follow-up of 39 months. Patients were censored at transplantation or when completing the follow-up period, with no loss of follow-up in any patient. The study exclusion criteria were formerly diagnosed or present signs of hyper- or hypothyroidism, as well as inflammatory illness, malignancy, use of drugs that alter thyroid function (amiodarone, propranolol, lithium) and unwillingness to participate. When we began our study, there were 105 patients, but after the baseline measurements were performed, 11 patients had to be excluded due to subclinical hypothyroidism (TSH ≥ 5 mIU/L) and clinically unrecognized inflammatory illness (CRP >30 mg/L). There remained 94 patients, 50 (53.2%) males and 44 (46.8%) females, median age 64 years, interquartile range (IQR) 57.3-76. Patient characteristics are shown in Table 1. The study protocol was approved by Ethics Committees of the Sestre milosrdnice University Hospital Centre from Zagreb and Dr Tomislav Bardek General Hospital from Koprivnica. A signed informed consent was obtained from each patient.

Methods

Hemodialysis patients were dialyzed three times weekly for four hours, through either an arteriovenous fistula or central venous catheter, using a polysulfone dialyzer 1.6-1.8 m², bicarbonate dialysis solution with dialysate flow 500 mL/min and blood flow rate 300 mL/min. The Kt/V as a measure of dialysis adequacy was checked weekly and targeted above 1.2. Blood was drawn before the start of hemodialysis treatment from the inserted dialysis needle or the arterial port of dialysis circuit, before contact of blood with dialyzer and before heparin administration. Peritoneal dialysis patients were treated with four 1.5- to 2-liter exchanges four times *per day* using standard dialysates containing glucose and icodextrin. Using the mentioned dialysis

Table 1. Patient demographic and anthropometric characteristics

Age (years)	64 IQR (57.3-76)
Gender:	
male	50/94 (53.2%)
female	44/94 (46.8%)
Dialysis type:	
hemodialysis	89/94 (94.7%)
peritoneal dialysis	5/94 (5.3%)
Type of venous access (HD patients):	
AV fistula	71/89 (79.8%)
catheter	18/89 (20.2%)
Vintage (length of time on dialysis in months)	27 IQR (14.3-60.8)
Kt/V	1.4 IQR (1.2-1.5)
Cause of ESRD:	
diabetic nephropathy	35/94 (37.2%)
hypertensive nephropathy	21/94 (22.3%)
chronic pyelonephritis	15/94 (16%)
polycystic disease	9/94 (9.6%)
obstructive uropathy	4/94 (4.3%)
post-ischemic nephropathy	3/94 (3.2%)
other	7/94 (7.4%)
Smoking status:	
non-smokers	72/94 (76.6%)
previous smokers	7/94 (7.4%)
active smokers	15/94 (16%)
Body height (cm)	165 IQR (158-173.8)
Body weight (kg)	74 IQR (62-85.1)
Body mass index (kg/m ²)	26.1 IQR (23-31.8)
Percentage of body fat (%)	19 IQR (15-24.8)
Charlson comorbidity index	6 IQR (4-7)

IQR = interquartile range; HD = hemodialysis; AV = arteriovenous; Kt/V = measure of dialysis adequacy; ESRD = end-stage renal disease; cm = centimeter; kg = kilogram; kg/m² = kilogram *per* cubic meter

prescription, the total Kt/V urea was aimed at minimum 1.7 *per* week.

At the beginning of the study, data on age, gender, type of dialysis, type of dialysis access, disease that caused ESRD, smoking habits and vintage (the length of time being treated with dialysis measured in months) were collected. Patients were measured for their body height (cm), weight (kg), body mass index (BMI, kg/m²) and percentage of fat tissue (using a standard caliper, in millimeters; skinfold thickness was measured at the rear part of the upper arm, two centi-

Table 2. Baseline laboratory parameters

RBC (x10e12/L)	3.5 IQR (3.3-3.8)
Hemoglobin (g/L)	109±12.4
Hematocrit (L/L)	0.33±0.04
MCV (fL)	94.9±5.2
WBC (x10e9/L)	6.5±1.9
Platelets (x10e9/L)	176 IQR (138.3-208.5)
Uric acid (μmol/L)	327.2 IQR (296-370)
Creatinine (μmol/L)	662.1±196.7
Total cholesterol (mmol/L)	4.1±0.8
HDL cholesterol (mmol/L)	1.12 IQR (0.9-1.4)
LDL cholesterol (mmol/L)	2.5 IQR (2.1-2.9)
Triglycerides (mmol/L)	1.4 IQR (0.9-2)
Calcium (mmol/L)	2.2±0.2
Phosphates (mmol/L)	1.5 IQR (1.1-1.8)
Serum iron (μmol/L)	12 IQR (9.7-15.2)
UIBC (μmol/L)	24.8±9
TIBC (μmol/L)	36.4 IQR (32.8-41.3)
Transferrin saturation (%)	32 IQR (25.5-43.6)
Total protein (g/L)	65.3±5.5
Albumin (g/L)	38.3±3.5
CRP (mg/L)	5.7 IQR (2-10.6)
Ferritin (ng/mL)	631.4 IQR (291-746.8)
PTH (pg/mL)	249 IQR (131.3-425)
Total T3 (nmol/L)	1.1 IQR (1-1.3)
fT3 (pmol/L)	2.3 IQR (2.1-2.5)
Total T4 (nmol/L)	64.1 IQR (55.5-74.1)
fT4 (pmol/L)	12±1.7
TSH (mIU/L)	1.5±0.7

IQR = interquartile range; RBC = red blood count; MCV = mean corpuscular volume; WBC = white blood cell count; HDL = high-density lipoprotein; LDL = low-density lipoprotein; UIBC = unsaturated iron binding capacity; TIBC = total iron binding capacity; CRP = C-reactive protein; PTH = parathyroid hormone; T3 = triiodothyronine; fT3 = free triiodothyronine; T4 = thyroxine; fT4 = free thyroxine; TSH = thyroid-stimulating hormone

meters laterally of the umbilicus and at the front part of the thigh; it was measured at the beginning of dialysis treatment, on the second dialysis in the week). Comorbidity was evaluated using modified Charlson comorbidity index (a method of predicting mortality by classifying or weighting comorbidities), without patient age included, as it was considered separately.

Laboratory data obtained at the beginning of the second weekly hemodialysis session and the regular monthly check-up were considered baseline values in

PD patients (Table 2). Plasma analyses of thyroid hormones and TSH were performed using Abbott commercially available Abbott assays (Abbott Laboratories, Zagreb, Croatia). All other biochemical analyses were performed on an Olympus AU2700 analyzer using original Beckman Coulter assays (Beckman Coulter, Zagreb, Croatia).

Statistical analysis

The normality of distribution of numerical variables was tested using the Kolmogorov-Smirnov test. Normally distributed numerical variables were expressed as arithmetic mean \pm standard deviation (SD), and were compared between the groups using the T-test. Non-normally distributed numerical variables were expressed as median and IQR, and were compared between the groups using the Mann Whitney U test. Correlation between numerical variables was assessed using Pearson or Spearman correlation depending on their normality of distribution. Categorical variables were expressed as number and proportion, and were compared between the groups using the χ^2 -test or Fisher exact test when appropriate. Survival analyses were based on the Kaplan-Meier method. Univariate and multivariate analysis of factors associated with survival of patients was performed using the Cox regression analysis. ROC curve analysis using survival status as a classification variable was performed to determine optimal cut-off values for numerical variables. The level of statistical significance was set at $p < 0.05$. All analyses were performed using the MedCalc Statistical software, version 17.8.1 (MedCalc Software bvba, Ostend, Belgium).

Results

Thyroid hormones and TSH and their clinical and laboratory correlations

The mean TSH value was 1.5 ± 0.7 mIU/L. Higher TSH was statistically significantly associated with lower uric acid (Rho -0.22, $p = 0.033$), lower unsaturated iron binding capacity (UIBC) (Rho -0.25, $p = 0.014$) and higher transferrin saturation (Rho 0.22, $p = 0.033$). In our cohort of patients with normal TSH values, there was no statistically significant association of TSH with other thyroid hormones.

The median total T3 value was 1.1 nmol/L, IQR (1-1.3). Higher total T3 was statistically significantly associated with younger age (Rho -0.25, $p = 0.017$), higher body weight (Rho 0.2, $p = 0.049$), higher red blood cell count (RBC) (Rho 0.24, $p = 0.021$), lower mean corpuscular volume (MCV) (Rho -0.26, $p = 0.010$), higher albumin (Rho 0.27, $p = 0.008$), lower ferritin (Rho -0.22, $p = 0.031$), higher fT3 (Rho 0.35, $p = 0.001$) and higher total T4 (Rho 0.34, $p = 0.001$).

The median fT3 value was 2.3 pmol/L, IQR (2.1-2.5). Higher fT3 was statistically significantly associated with peritoneal dialysis (median 4.36 *vs.* 2.23, $p < 0.001$), younger age (Rho -0.24, $p = 0.020$), lower Charlson comorbidity index (Rho -0.35, $p = 0.001$), higher body height (Rho 0.34, $p = 0.001$), higher body weight (Rho 0.33, $p = 0.001$), higher uric acid (Rho 0.27, $p = 0.010$), higher UIBC (Rho 0.36, $p < 0.001$), higher total iron binding capacity (TIBC) (Rho 0.41, $p < 0.001$), lower transferrin saturation (Rho -0.21, $p = 0.044$), higher albumin (Rho 0.25, $p = 0.014$), higher total T3 (Rho 0.35, $p = 0.001$), higher total T4 (Rho 0.36, $p < 0.001$) and higher fT4 (Rho 0.41, $p < 0.001$).

The median total T4 value was 64.1 nmol/L, IQR (55.5-74.1). Higher total T4 was statistically significantly associated with peritoneal dialysis (median 88.8 *vs.* 62.6, $p = 0.001$), higher Kt/V (Rho 0.29, $p = 0.005$), lower serum iron (Rho -0.25, $p = 0.017$), higher UIBC (Rho 0.31, $p = 0.003$), higher TIBC (Rho 0.21, $p = 0.039$), lower transferrin saturation (Rho -0.31, $p = 0.003$), lower parathyroid hormone (PTH) (Rho -0.22, $p = 0.038$), higher total T3 (Rho 0.34, $p = 0.001$), higher fT3 (Rho 0.36, $p < 0.001$) and higher fT4 (Rho 0.86, $p < 0.001$).

The mean fT4 value was 12 ± 1.7 pmol/L. Higher fT4 was statistically significantly associated with peritoneal dialysis (median 14.4 *vs.* 11.72, $p = 0.003$), higher Kt/V (Rho 0.25, $p = 0.015$), lower serum iron (Rho -0.21, $p = 0.042$), higher UIBC (Rho 0.26, $p = 0.011$), lower transferrin saturation (Rho -0.28, $p = 0.006$), lower PTH (Rho -0.25, $p = 0.014$), higher fT3 (Rho 0.41, $p < 0.001$) and higher total T4 (Rho 0.86, $p < 0.001$).

Survival of patients

The median follow up of our patients was 39 months. Forty-two patients died during the follow up period. The most common causes of death were sudden cardiac death in 17/94 (40.5%), sepsis in 17/94

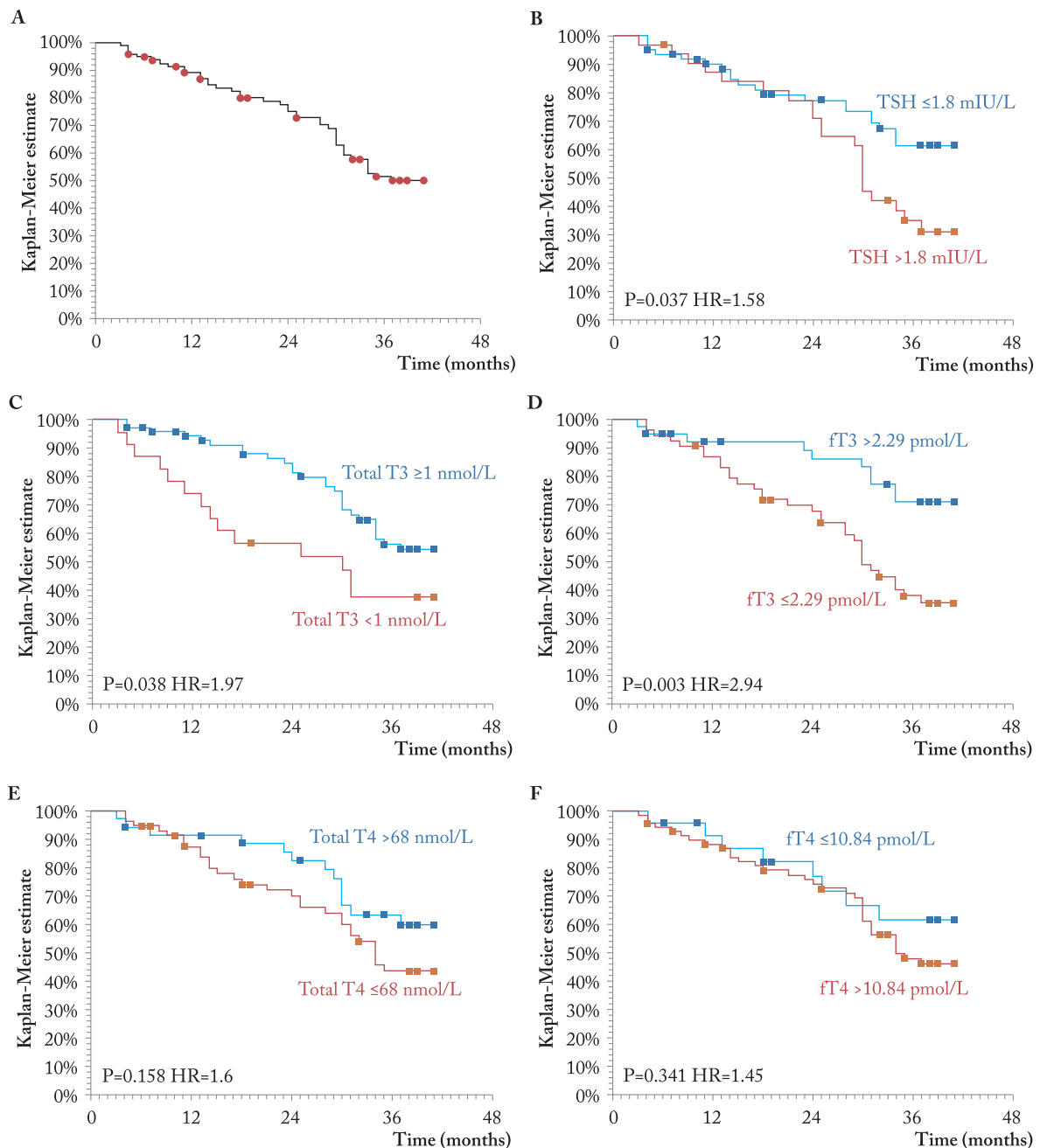


Fig. 1. (A) Survival curve for all patients; (B) higher TSH; (C) lower total T3; and (D) lower fT3 were associated with inferior survival; (E) total T4; and (F) fT4 were not significantly associated with survival.

*statistically significant at $p < 0.05$; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; fT3 = free triiodothyronine; T4 = thyroxine; fT4 = free thyroxine; HR = hazard ratio

(40.5%), disseminated malignant disease in 2/42 (4.8%), cerebrovascular insult in 2/42 (4.8%) patients, and hepatocellular carcinoma, myocardial infarction, suspected pulmonary embolism and unknown cause of death in one patient each. Survival curve for all pa-

tients is shown in Figure 1A. Median survival was not reached; the 3-year survival rate was 51.4%.

Optimal cut-off values with best survival discriminatory properties for thyroid hormones were determined using ROC curve analysis. The cut-off for TSH

Table 3. Cox regression analysis investigating associations of thyroid hormones with survival

Variable	HR; 95% CI	p
Total T3 <1 nmol/L	HR 2.26 95% CI [1.15-4.44]	0.019*
fT3 ≤2.29 pmol/L	HR 2.83 95% CI [1.36-5.88]	0.005*
TSH >1.8 mIU/L	HR 2.03 95% CI [1.06-3.9]	0.033*
Total T4 ≤68 nmol/L	HR 1.56 95% CI [0.77-3.19]	0.218
fT4 >10.84 pmol/L	HR 1.79 95% CI [0.76-4.22]	0.181

*statistically significant at $p < 0.05$; 95% CI = 95% confidence interval; HR = hazard ratio; T3 = triiodothyronine; fT3 = free triiodothyronine; TSH = thyroid-stimulating hormone; T4 = thyroxine; fT4 = free thyroxine

was set at >1.8 mIU/L. Although all patients had TSH values within the reference range, patients with higher TSH values experienced shorter survival in comparison to those with lower TSH values at baseline, as shown in Figure 1B (hazard ratio (HR) 1.58, $p = 0.037$). Both groups experienced similar survival for the period of 2 years, then survival curves started to diverge. The cut-off for total T3 was set at <1 nmol/L; patients with lower total T3 levels had inferior survival in comparison to patients with higher (normal) total T3 levels, as shown in Figure 1C (HR 1.97, $p = 0.038$). The cut-off for fT3 was set at >2.29 pmol/L; patients with lower fT3 similarly had inferior survival in comparison to patients with higher (normal) fT3 values, as shown in Figure 1D (HR 2.94, $p = 0.003$). The cut-off values obtained for total T4 and fT4 were <86 nmol/L and >10.84 pmol/L, respectively. Total T4 ($p = 0.158$) and fT4 ($p = 0.341$) were not statistically significantly associated with survival in our cohort of patients.

We compared prognostic properties of different thyroid hormones in a Cox regression model containing TSH, total T3, fT3, total T4 and fT4, as shown in Table 3. Low total T3 (HR 2.26, $p = 0.019$), low fT3 (HR 2.83, $p = 0.005$) and high-normal TSH (HR 2.03, $p = 0.033$) each bore an independent prognostic potential as they were able to retain statistical significance and predict survival independently of each other.

Other parameters that were univariately associated with survival were catheter as venous access (HR 2.44, $p = 0.008$), age (HR 1.05, $p = 0.001$), vintage (HR 1.01,

Table 4. Cox regression model investigating associations of total T3, fT3, TSH and other univariately significant variables with survival

Variable	HR; 95% CI	p
Total T3 <1 nmol/L	HR 2.19 95% CI (1.05-4.6)	0.038*
fT3 ≤2.29 pmol/L	HR 1.61 95% CI (0.68-3.83)	0.283
TSH >1.8 mIU/L	HR 1.67 95% CI (0.86-3.24)	0.128
Catheter as venous access	HR 2.76 95% CI (1.15-6.62)	0.023*
Age (years)	HR 1.03 95% CI (0.99-1.06)	0.122
Male gender	HR 1.39 95% CI (0.65-2.98)	0.398
Vintage (months)	HR 1.01 95% CI (1-1.02)	0.014*
Charlson comorbidity index	HR 1.28 95% CI (1.05-1.57)	0.017*
Body height (cm)	HR 1 95% CI (0.97-1.03)	0.996
Albumin (g/L)	HR 0.94 95% CI (.82-1.08)	0.383
CRP (mg/L)	HR 1.01 95% CI (0.97-1.05)	0.624

*statistically significant at $p < 0.05$; 95% CI = 95% confidence interval; HR = hazard ratio; T3 = triiodothyronine; fT3 = free triiodothyronine; TSH = thyroid-stimulating hormone; CRP = C-reactive protein

$p = 0.034$), Charlson comorbidity index (HR 1.39, $p < 0.001$), body height (HR 0.07, $p = 0.021$), albumin (HR 0.88, $p = 0.008$) and CRP (HR 1.04, $p = 0.006$). We further investigated prognostic properties of thyroid hormones in a Cox regression analysis model including total T3, fT3, TSH and other factors mentioned above that were univariately associated with survival and gender, as shown in Table 4. Low total T3 (HR 2.19, $p = 0.038$), catheter as venous access (HR 2.76, $p = 0.023$), higher vintage (HR 1.01, $p = 0.014$) and higher Charlson comorbidity index (HR 1.28, $p = 0.017$) remained statistically significantly associated with inferior survival.

Discussion

Study results showed that in our group of steady-state dialysis patients, total T3 seemed to be an inde-

pendent predictor of inferior survival among thyroid hormones. It could identify patients at an increased risk of death even after adjustment for other prognostically relevant variables. It was interesting to see that the higher values of TSH, when using only thyroid hormones in the analysis, were a significant mortality risk, even though all the TSH values were in the reference range since we were focusing exclusively on the low T3 syndrome. However, when we included other statistically relevant confounding factors, TSH values lost their significance.

The results from earlier studies showed that serum albumin and CRP were significantly related with all-cause mortality¹³ and that the CRP levels were a consistent predictor of survival in hemodialysis populations¹. However, in our study, after further adjustment for fT3, T3, TSH and other significant confounding factors, the impact of CRP and albumin on survival disappeared due to overlapping prognostic properties. We concluded that, although it is known that low T3 syndrome and PEW are interrelated^{15,16}, in our group of patients T3 had greater influence on survival.

It has been recognized that all-cause and cardiovascular mortality is consistently higher in long-term dialysis patients with derangements in thyroid function test results. It is a question whether it would be cost-effective to screen for thyroid function among patients with ESRD²⁰. When validating a potential new prognostic biomarker, there are four criteria to consider. The first one is accuracy, which is the ability to reliably identify individuals at a greater risk of the adverse clinical outcome of interest. The second one is simplicity (for example, ease of measurement). The third one is the cost (biomarkers should be inexpensive and cost-effective), and the last one is the relevance of the information provided by the biomarker²¹. According to the results of our study, and to the available scientific information gathered so far, it is our opinion that T3 should be considered as an important novel prognostic factor that should be taken into consideration when analyzing survival chances of patients on dialysis.

Furthermore, in our study, using a central venous catheter (CVC) as vascular access in hemodialysis patients proved to be a significant mortality risk factor. This finding is in accordance with the results of another study comparing different types of vascular access (CVC, arteriovenous fistulas (AVF) and arterio-

venous grafts (AVG))²². In this study, the survival rate among patients in whom hemodialysis was initiated with AVF was significantly higher than that in patients in whom hemodialysis was initiated with AVG or CVC²². Patients who started hemodialysis and were using a venous catheter were at a 47% higher death risk compared with patients who were using an AVF. This association remained unaltered after adjustment for the potential confounding factors and after accounting for frequent changes in access type over time²³. What is interesting about our finding is that, to the best of our knowledge, there has not been a study that investigated the correlation of thyroid hormones with mortality in dialysis patients, alongside other mortality risk factors, which also included the hemodialysis access. For this reason, we would suggest that hemodialysis vascular access be taken into account as an essential risk factor in the future survival studies.

The results of our study confirmed once more that Charlson comorbidity index is a valid tool for assessing comorbidity burden in dialysis patients²⁴⁻²⁶. Also, following previous studies²⁷, the dialysis vintage is a significant mortality risk.

Risk prediction models can be used to inform the patients undergoing renal replacement therapy about their survival chances. Hemke *et al.* showed that a simple model based only on registry data could be enhanced by adding readily available clinical parameters, such as cholesterol, phosphate, and albumin²⁸. The associations among the main risk factors for death in hemodialysis patients are complex. A study by Kanda *et al.* showed that simultaneous evaluation of multiple risk factors could accurately assess patient prognosis and identify patients at an increased risk of death¹⁹. Based on the results of our study, we agree with the conclusions of the studies above regarding the necessity of multiple mortality risk factor approach in assessing prognosis of ESRD patients.

Our study had some limitations. The cohort had less than 100 patients, and the median follow up of our patients was 39 months. The question remains whether the parameters that were statistically significant would remain significant if the study group was larger and the follow up longer. Furthermore, we did not consider blood pressure as a confounder. It was proven that lower blood pressure in patients on hemodialysis (predialysis systolic <110 mm Hg), as well as higher blood pressure (predialysis systolic 150-159 mm Hg) was as-

sociated with higher mortality²⁹. Finally, it is a question whether measures that we included in the study, such as serum albumin, BMI and percentage of fat tissue, were adequate to assess completely the presence of PEW. We were unable to assess dietary protein intake or dietary energy intake, which are considered as components of this syndrome¹².

In conclusion, T3 seems to be the most reliable predictor of inferior survival among thyroid hormones. It could identify patients at an increased risk of death even after adjustment for other prognostically relevant variables, and it should be considered as an important mortality risk factor in evaluating the prognosis of ESRD patients.

Acknowledgments

The authors wish to express their appreciation to the whole dialysis nursing staff at the Sestre milosrdnice University Hospital Centre from Zagreb (Marica Prša, Head Nurse) and Dr Tomislav Bardek General Hospital from Koprivnica (Dražen Buhaneć, Head Medical Technician) (clinical studies), as well as to Ivana Čelap, MSc, and Professor Nada Vrkić, PhD (biochemical analysis).

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Sažetak

POVEZANOST SINDROMA NISKOG TRIJODTIRONINA, PROTEINSKO ENERGETSKE POTHRANJENOSTI I KRONIČNE UPALE SA SMRTNOŠĆU PREVALENTNIH DIJALIZNIH BOLESNIKA

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Cilj je bio istražiti prognostička svojstva sindroma niskog trijodtironina, proteinsko energetske pothranjenosti i kronične upale te drugih poznatih rizičnih čimbenika sa smrtnošću prevalentnih dijaliznih bolesnika. Ukupno 94 prevalentnih dijaliznih bolesnika prospektivno je praćeno kroz medijan od 39 mjeseci. Na početku istraživanja sakupljeni su demografski, antropometrijski i biokemijski parametri. Učinjena je univarijatna te multivarijatna analiza primjenom Coxove regresijske analize. Kako bismo odredili optimalne granične vrijednosti numeričkih varijabla primijenjena je ROC analiza krivulje koristeći preživljenje kao klasifikacijsku varijablu. U našoj populaciji bolesnika su nizak ukupni trijodtironin (*hazard ratio* (HR) 2,19; $p=0,038$), kateter kao vaskularni pristup (HR 2,76; $p=0,023$), duži *vintage* (HR 1,01; $p=0,014$) i viši Charlson indeks komorbiditeta (HR 1,28; $p=0,017$) bili statistički značajno povezani s lošijim preživljenjem. U našoj skupini stabilnih dijaliznih bolesnika ukupni trijodtironin je među hormonima štitnjače bio najjači predskazatelj lošijeg preživljenja. Također, i nakon prilagodbe za druge prognostički značajne varijable vrijednost trijodtironina se i dalje može koristiti u prognozi bolesnika na dijalizi. Nakon daljnje analize prilagođene za druge značajne čimbenike rizika utjecaj C-reaktivnog proteina i albumina na smrtnost je nestao zbog prognostičkih svojstava koja se podudaraju. Zaključno, smatramo da je ukupni trijodtironin bio neovisan prognostički čimbenik u našoj skupini bolesnika.

Ključne riječi: *Dijaliza; Netireoidna bolest štitnjače; Upala; Rizični čimbenici; Hrvatska*