Risk factors for cardiovascular hospitalization in hemodialysis patients

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Summary. *The aim of this study was to evaluate the risk factors for cardiovascular hospitalization in hemodialysis patients.*

Materials and methods. A cross-sectional cohort analysis of risk factors during one census month (November) and one-year follow-up for cardiovascular hospitalization rates during 5 consecutive years (2002–2006) in all end-stage renal disease patients hemodialyzed in Kaunas region was carried out. During the census month, we collected data on patient's age and sex, disability status, comorbidities, anemia control, malnutrition and inflammation, calcium-phosphorus metabolism, and patient's compliance with prescribed medications. We analyzed 559 patients during 1163 patient-years of observation. Patients were considered as new patients every year (1520 cases). Kaplan-Meier method and Cox regression analysis were used to evaluate time to first hospitalization.

Results. The mean number of cardiovascular hospitalizations was 0.31 per patient-year at risk, the total days of cardiovascular hospitalizations per patient-year at risk were 3.93, and the mean length of one hospitalization was 13.2±12.9 days. Cardiovascular diseases were the most frequent cause of hospitalization (25% of all hospitalizations). The relative risk of cardiovascular hospitalization increased by 1.03 for every year of age, by 1.7 for worse disability status, by 1.4 for nonadherence to medications, by 1.1 for every additional medication prescribed to the patient. Cardiovascular hospitalization risk was decreased by 0.99 with a 1-g/L rise in hemoglobin level.

Conclusions. Older age, worse disability status, patient's noncompliance with medications, and higher number of medications used were associated with a higher risk for cardiovascular hospitalization. Higher hemoglobin level was associated with a lower risk for cardiovascular hospitalization.

Introduction

The world's disease profile is changing, and chronic diseases now account for majority of global morbidity and mortality. Chronic diseases now are the leading causes of death worldwide: there were approximately 58 million deaths worldwide in 2005, with 35 million deaths attributed to chronic diseases. It is estimated that about 50 million people will die from chronic diseases in the year 2020 worldwide (1, 2). The causes of chronic kidney diseases reflect this change and diabetes, together with hypertension, is now the major cause of end-stage renal disease (ESRD) (3). This is a huge financial burden for society, and the treatment of ESRD accounts for a large part of it (3–6). Hemodialysis (HD) is one of the options of renal replacement therapy. With growing life expectancy and better quality of the treatment, dialysis population becomes older with severe comorbidities and high risk for hospitalization. In the United States, hospitalization costs for ESRD patients account for 40–60% of total Medicare expenditures (7, 8). Therefore, it is necessary to evaluate the risk factors for hospitalization and to assess possibilities of outpatient treatment optimization and reduction of hospitalization rates in hemodialysis patients. Cardiovascular diseases are one of the most common causes of hospitalization in hemodialysis patients (8–12).

The aim of this study was to evaluate risk factors for cardiovascular hospitalization in hemodialysis patients.

Materials and methods

We conducted a cross-sectional cohort study with

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prospective follow-up in the Department of Nephrology, Hospital of Kaunas University of Medicine, Lithuania, and in all the dialysis centers of Kaunas region. Kaunas Regional Ethics Committee for Biomedical Research approved the study. During the census month (November) of each observation year, we analyzed outpatient case records of ESRD patients hemodialyzed in all centers in Kaunas region in 2002–2006 to collect data about age and sex, the cause of ESRD, disability status, comorbidities, anemia control, malnutrition and inflammation, calcium-phosphorus metabolism, and patient's compliance. According to functional impairment (disability status), the patients were divided into the following groups: patients with normal physical activity, patients who needed assistance, and patients who needed constant care. Comorbidities were evaluated by the number of different organ systems affected with separate evaluation of diabetes mellitus (DM), ischemic heart disease (IHD), and heart failure (New York Heart Association, NYHA, classification, and heart ejection fraction on ultrasound). Hypertension control was estimated by mean blood pressure (BP) before and after HD (the mean of last 3 HD sessions was calculated). The control of anemia was assessed by hemoglobin and ferritin level. Calcium-phosphorus metabolism was evaluated by serum calcium, phosphorus, and parathormone levels. Malnutrition and inflammation was estimated by patient's weight, body mass index, serum creatinine, CRP, and albumin level before HD. Urea before and after HD session was measured, and Kt/V (a measure of dialysis adequacy expressed by the treatment-related urea reduction ratio) was calculated in order to evaluate HD quality. The patient's measures of nonadherence used in this study were skipping or shortening of one or more hemodialysis sessions in census month, hyperkalemia and hyperphosphatemia, interdialytic weight gain, and compliance with medications assessed by patient's doctor. These data were collected in November of each year, and then patients were followed up for 12 months prospectively for cardiovascular hospitalization, expressed as time to hospitalization, and as the number of hospitalizations and total days of hospitalization during the following year. We analyzed 559 patients during 1163 patient-years of observation. Patients were considered as new patients every year (1520 cases). Only patients dialyzed during more than 3 months were included into statistical analysis.

To assess whether the data obtained in Kaunas region were representative for the whole Lithuania, we collected data on demographic factors, routinely screened laboratory tests, and the number of hospi-talizations per year in all other dialysis centers in Lithuania.

Statistical data analysis. SPSS 13.0 and STATISTICA 5.5A statistical packages were used to analyze the data. For evaluation of continuous variables, the statistical mean and standard deviation were calculated. Differences between groups were assessed by the Mann-Whitney-Wilcoxon test and Pearson chi-square test as appropriate. Hospitalization rate was calculated as the total number of hospitalizations per patient-year at risk. Kaplan-Meier method and Cox regression analysis were used to evaluate time to the first hospitalization. Cutoff values were detected by maximal χ^2 values, and the area under the receiver operating characteristic (ROC) curves. Statistical significance was assumed at $P<0.05$.

Results

In total, we analyzed 559 patients during 1163 patient-years of observation. Patients were considered as new patients every year (1520 cases). Complete data about laboratory test results, disability status, patient's compliance, and nutritional status were assessed in 1255 cases. Women were significantly older than men (59.2±15.8 years versus 57±15.4; P=0.005).

The mean number of cardiovascular hospitalizations was 0.31 per patient-year at risk, the total days of cardiovascular hospitalizations per patient-year at risk were 3.93, and the mean length of one hospitalization was 13.2±12.9 days. Cardiovascular diseases were the most frequent cause of hospitalization (25% of all hospitalizations).

When testing patients' comorbidities and disability status, the univariate analysis showed that worse disability status, older age, higher systolic BP before HD, worse ejection fraction on ultrasound, worse NYHA functional status, and IHD were associated with more frequent cardiovascular hospitalizations. These factors were included into the first Cox regression model (Table). This model selected age, disability status, and BP before HD to be the most important ones, and they were enrolled into the final model. In the second step, we constructed the model including laboratory tests, which were relevant for cardiovascular hospitalization in the univariate analysis: lower creatinine, hemoglobin, albumin, and Kt/V were associated with more frequent hospitalizations. This model selected hemoglobin and Kt/V as the most important factors, and they were included into the final model (Table). Univariate analysis also revealed more frequent cardiovascular hospitalizations in patients taking more medications and noncompliant

Table. Cox regression analysis model for evaluation of risk factors for cardiovascular hospitalization

Model 1			Model 2			Model 3	
Factors	**P**		**Factors**	**P**		**Factors**	**P**
Age	<0.001		Age	<0.001		Age	<0.001
Disability	<0.001		Creatinine	0.8		Nonadherence to medications	<0.001
Systolic BP before HD	0.007		Hemoglobin	0.01		Number of medications	0.004
Ischemic heart disease	0.08		Albumin	0.09			
NYHA (class 3–4)	0.12		Kt/V	0.006			
Ejection fraction	0.08						

Final model			
Factors	**Coefficient**	**P**	**Relative risk (95% CI)**
Age	0.03	<0.001	1.03 (1.02–1.04)
Disability	0.5	<0.001	1.7 (1.3–2.3)
Systolic BP before HD	0.006	0.085	1.0 (0.99–1.012)
Hemoglobin	−0.011	0.04	0.99 (0.98–1.0)
Kt/V	−0.48	0.08	0.6 (0.37–1.06)
Nonadherence to medications	0.34	0.04	1.4 (1.02–1.95)
Number of medications	0.09	0.003	1.1 (1.03–1.16)

with prescribed medications by doctor's assessment. These factors together with age were included into the third Cox model (Table).

The final Cox regression model showed that the relative risk for cardiovascular hospitalization increased by 1.03 for every year of age, by 1.7 for worse disability status, by 1.4 for nonadherence to medications, by 1.1 for every additional medication prescribed to the patient. Cardiovascular hospitalization risk was decreased by 0.99 with a 1-g/L rise in hemoglobin level.

Cutoff values were calculated for the most important risk factors for cardiovascular hospitalization. In our study, risk factors for cardiovascular hospitalization of HD patients were the following: patient's age of ≥60 years, disability status, need for assistance or constant care, hemoglobin of ≤100 g/L, nonadherence to medications, and the simultaneous use of more than 7 medications.

In our study, we found that 39.9% of HD patients had 0–1 risk factor, 53.6%, 2–3 risk factors, and 7.5%, 4–5 risk factors. The relative risk of cardiovascular hospitalization was increased by 2.3 (95% CI, 1.6–3.1; $P<0.001$) in HD patients with 2–3 risk factors and by 4.6 (95% CI, 3.0–7.2; $P<0.001$) in HD patients with 4–5 risk factors as compared to patients with 0–1 risk factor. Associations between the number of risk factors and cardiovascular hospitalization are shown in Fig.
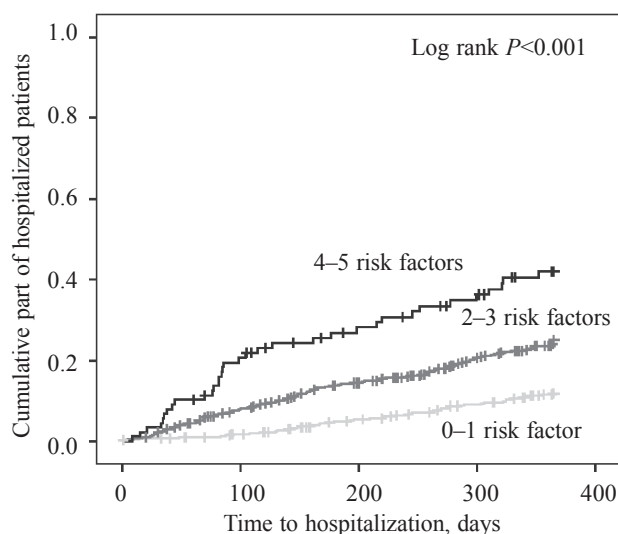

Fig. Associations between the number of risk factors and cardiovascular hospitalization

Kaplan-Meier curves show that a cumulative part of patients hospitalized for cardiovascular diseases increases with the increasing number of risk factors.

In order to evaluate whether HD patients in Kaunas region represent the general HD population of Lithuania, demographic factors, routinely screened laboratory tests, medications prescribed, and overall hospitalization rates were compared between these groups in the years 2002–2005. No systematic differences in demographic data, laboratory test results,

and hospitalization rate were found between HD patients in Kaunas region and Lithuanian HD patients, and hemodialysis patients in Kaunas region are representative of the general Lithuanian hemodialysis population.

Discussion

The Dialysis Outcomes and Practice Patterns Study (DOPPS) reported that in five European countries, 17.6–37.4% of all hospitalizations were due to cardiovascular diseases, and cardiovascular hospitalization rate was 0.19–0.4 hospitalizations per patient-year at risk. These diseases were the most frequent cause of hospitalization in Germany, France, and Spain (13). The study conducted in Lenox Hill Hospital, New York, in 2003 revealed that cardiovascular diseases were the major cause of hospital admission for HD patients. Cardiovascular diseases accounted for 49% of chronic and 40% of acute admissions. Diabetes mellitus, hypertension, and ischemic heart disease were the risk factors for cardiovascular hospitalization. Associations between cardiovascular hospitalization and laboratory tests were not tested in this study (14). In contrast, data from two hospitals in Denver showed that cardiovascular hospitalizations account only for 13% of all hospitalizations (0.25 hospitalizations per patient-year) (15). According to our data for Lithuanian HD patients, cardiovascular hospitalization rate was 0.31 hospitalizations per patient-year at risk and accounted for 25% of all hospitalizations. The Lithuanian Health Information Center declared that cardiovascular diseases were the most frequent cause of hospitalizations in general Lithuanian population (54.5 hospitalizations per 1000 residents, 0.0545 hospitalizations per resident) (16). Our data confirmed cardiovascular diseases being the most frequent cause also in Lithuanian HD population, but HD patients were hospitalized 5.7 times more frequently because of this reason.

The study by Chertow et al. carried out in the United States reported older age, DM, higher serum phosphorus, calcium, and ferritin concentrations, and lower bicarbonate concentration as the risk factors for cardiovascular hospitalization (17). Other study described age, white race, diabetes, lower body weight, higher serum phosphorus, PTH, ferritin and cholesterol concentrations, lower serum albumin and hemoglobin concentrations as being the risk factors for cardiovascular hospitalization (18). Relationship of increased serum calcium and phosphorus concentration (higher than recommended in the international guidelines) with more frequent cardiovascular hospitalization was also confirmed by other authors (19). Cardiovascular hospitalization rate was lower in incident HD patients with higher hematocrit values (20). Prolongation of weekly hemodialysis time from 30 to 48 hours per week was associated with the reduction in cardiovascular hospitalizations from 0.5 to 0.17 cardiovascular hospitalizations per patient-year (21). "Reverse" epidemiology of cardiovascular risk factors was described in HD patients: conventional risk factors for cardiovascular disease and mortality in general population, such as obesity, hypercholesterolemia, and hypertension, appear to be protective features that are associated with a greater survival among dialysis patients (22).

Our results revealed that older age, disability, anemia, nonadherence with prescribed medications, and higher number of medications used were risk factors for cardiovascular hospitalization in Lithuanian HD patients. None of these factors had a high sensitivity or specificity to prognosticate hospitalization but they all acting together significantly increased hospitalization risk. We confirmed literature data about the influence of older age and anemia on higher cardiovascular hospitalization rate (18, 20), but we could not confirm the influence of diabetes, disturbances of calcium and phosphorus metabolism, lower albumin, ischemic heart disease, and hypertension (14, 18). To our knowledge, higher cardiovascular hospitalization rate in HD patients with disability, HD patients nonadherent with medications, and HD patients using higher number of medications has not been reported in the literature before.

The number of medications used depends on the number of comorbid diseases. On the other hand, when a patient uses more medications, there is a higher possibility of adverse reactions and nonadherence with prescribed medications. Our data show that patient's compliance with prescribed medication treatment is very important – nonadherence increased a cardiovascular hospitalization risk by 1.4.

Conclusions

Older age, worse disability status, patient's noncompliance with prescribed medications, and higher number of medications used was associated with a higher risk of cardiovascular hospitalization. Higher hemoglobin level was associated with a lower risk of cardiovascular hospitalization.

Hemodializuojamų ligonių hospitalizavimo dėl širdies ir kraujagyslių ligų rizikos veiksniai

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Raktažodžiai: hemodializė, hospitalizavimas, širdies ir kraujagyslių ligos.

Santrauka. *Tyrimo tikslas.* Įvertinti hemodializuojamų ligonių hospitalizavimo dėl širdies ir kraujagyslių ligų rizikos veiksnius.

Tyrimo medžiaga ir metodai. Išanalizuotos ambulatorinės kortelės visų galutinės stadijos inkstų nepakankamumu sergančių ligonių, kurie buvo hemodializuoti visuose Kauno krašto hemodializės centruose 2002–2006 m. Kohortinio momentinio tyrimo metu kiekvienų metų lapkričio mėnesį rinkti duomenys apie ligonio amžių ir lytį, neįgalumo būklę, gretutines ligas, anemijos laipsnį, mitybos ir uždegimo žymenis, kalcio ir fosforo apykaitą, gydymo režimo laikymąsi, toliau pacientus stebint 12 mėn. dėl hospitalizavimų. Į tyrimą įtraukti 559 pacientai (iš viso 1163 stebėjimo metai). Kiekvienais metais tiriami ligoniai vertinti kaip nauji ir atlikta suminė penkerių metų duomenų analizė (iš viso 1520 atvejai). Rizikos veiksniams įvertinti atlikta daugiamatė Cox regresinė analizė ir įvertinta trukmė iki pirmojo hospitalizavimo.

Rezultatai. Hospitalizavimų dėl širdies ir kraujagyslių ligų skaičius buvo 0,31 hospitalizavimo/ligoniui/ rizikos metams, lovadienių skaičius – 3,93 dienos/ligoniui/rizikos metams, vieno hospitalizavimo trukmė – 13,2±12,9 dienos. Širdies ir kraujagyslių ligos buvo dažniausia hemodializuojamų ligonių hospitalizavimo priežastis (25 proc. visų hospitalizavimų). Santykinė stacionarinio gydymo dėl širdies ir kraujagyslių ligų rizika padidėjo 1,03 su kiekvienais amžiaus metais, 1,7 ligonio reikalinga pagalba arba slauga; 1,4 – vaistus vartoja netvarkingai arba visai jų nevartoja; 1,1 – kiekvienam papildomam vartojamam medikamentui; sumažėjo 0,99 – hemoglobinui padidėjus 1 g/l.

Išvados. Vyresnis ligonio amžius, sunkesnė neįgalumo būklė, netvarkingas vaistų vartojimas ir didesnis vartojamų medikamentų skaičius didina hemodializuojamų ligonių hospitalizavimo dėl širdies ir kraujagyslių ligų riziką. Hospitalizavimo dėl širdies ir kraujagyslių ligų riziką mažina didesnė hemoglobino koncentracija kraujyje.

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