

Original article

## Sex-dependent differences in patients treated with regular hemodialysis

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### Summary

**Introduction.** The aims of the study were to find out sex differences among patients starting regular hemodialysis (HD) in 2014 and to check whether these differences change over a five-year period.

**Methods.** The retrospective five-year study included 35 patients (24 men; 11 women) starting HD in HD centers in Leskovac and Pirot in 2014. Demographic data, clinical data, laboratory findings, and medication used for examined patients were taken from medical records.

**Results.** A comparison of patients of different sexes at the beginning of the study showed that women were significantly older ( $70.55 \pm 13.27$  vs.  $58.88 \pm 15.27$  years), but diabetes and hypertension were more frequent causes of chronic kidney disease in men. Women had significantly lower body mass index and serum creatinine level than men in the first year of the study. During all five years, the HD adequacy index  $\text{spKt/V}$  was higher in women than in men, but the difference reached statistical significance only in the third year ( $1.4 \pm 0.2$  vs.  $1.2 \pm 0.2$ ). Serum iPTH level was higher in women than in men in almost the entire study period. There was no significant sex difference in blood pressure, type of vascular access, number of HD hours per week, in the percentage of patients who used erythropoiesis-stimulating agents or phosphate binders. During the study period 10 (42.7%) men and five (45.5%) women died and the most frequent causes of death were cerebrovascular and cardiovascular diseases.

**Conclusion.** The study revealed several differences between men and women on regular HD, but no treatment inequality was found.

**Keywords:** hemodialysis patients, sex differences, retrospective study

## Introduction

Around the world, there is a higher percentage of women than men in the general population, and as women live longer, their percentage increases in older age groups [1, 2]. Also, large screening studies have shown that more women than men have chronic kidney disease (CKD) [1, 3]. In contrast, worldwide, the higher percentage of men than women start renal replacement therapy [4, 5]. This is confirmed by The Registry on Renal Replacement Therapy patients in Serbia which shows that in recent years, 66% of patients who start hemodialysis in Serbia are men [6]. The causes of this sex disparity have been examined in several studies

and they are partly explained by biological but also social factors [7–9].

In the present study, we approached this problem from a different angle. The study aimed to compare the clinical characteristics, laboratory findings and the drug therapy used between men and women who started hemodialysis (HD) treatment in two centers in southern Serbia in 2014 and to check whether these differences changed over a five-year period. In addition, we checked whether sex-differences in patients treated in our two centers were different from those treated in other centers in Serbia.

## Methods

The retrospective five-year study included 35 patients starting regular HD in two HD centers in southern Serbia (Leskovac and Pirot) in 2014. During the study period, patients were on bicarbonate 4-hour HD using high-flux polysulfone membrane of size 1.3–1.8 m<sup>2</sup>. The Ethics Committee of the Leskovac General Hospital approved the implementation of the retrospective study at the meeting held on February 15, 2019. The decision was filed under number 330/2019.

We analyzed data of examined patients registered in medical records from the beginning of HD treatment in 2014 until patients' death, transfer to other renal replacement therapy (RRT) methods, transfer to another center or the end of the study. Treatment and control of anemia and mineral metabolism were carried out in accordance with the recommendations of the current KDIGO guidelines (<https://kdigo.org/guidelines/>). Laboratory analyzes were done in laboratories of local general hospitals using routine laboratory methods and iPTH by hemiluminescence assay (Diagnostic Product Corporation, USA). Most of laboratory analyzes were done quarterly, except blood cells (every month) and iPTH (twice a year). HD adequacy was

assessed by index single-pool urea Kt/V (sp-Kt/V), where K is the dialyzer urea clearance, t is HD treatment time, and V is the urea distribution volume of the patient equal to 60% weight for men, 50% for women and 45% for elderly women [10].

Descriptive statistics were presented as mean values and standard deviation for the continuous variables, or as frequencies for categorical variables. For the analysis Student's t-test and Chi-square-test were used as appropriate. The statistical package of the SPSS program Version 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp) was used for statistical analysis.

## Results

In two HD centers in southern Serbia, the HD center in Leskovac and Pirot, 152 patients were treated with regular HD at the end of 2014. That year, 35 patients started HD treatment and all were included in this retrospective longitudinal five-year study. Among them there were 24 men and 11 women, and at the beginning of the study, they differed significantly in age and underlying disease: women were significantly older, but diabetes and hypertension were more frequent underlying diseases in men (Table 1).

The clinical characteristics, HD parameters and the drug therapy of patients during examined period are shown in Table 2. Women had lower body mass index (BMI) than men and the difference was significant in the first two years of the study. There was no significant difference between men and women in blood pressure, type of vascular access, number of HD hours per week, or in the percentage of patients who used erythropoiesis stimulating agents (ESA) or phosphate binders. During all five years, the spKt/V was higher in women than in men, but the difference was generally insignificant.

Laboratory analyzes showed that women had significantly lower serum creatinine level in the first year of study, and higher serum iPTH level in almost the entire study period in comparison to men. In other laboratory findings, shown in table 3, there were no significant differences between patients of different sexes.

Out of the 24 men and 11 women who started HD in 2014, 11 men and five women were still on chronic HD at the end of 2018.

During the five-year period, one man underwent a kidney transplant, one man and one woman were transferred to the peritoneal dialysis, one man was transferred to another center, and 10 (42.7%) men and five (45.5%) women died (Figure 1). The causes of death were: cerebrovascular diseases in seven patients, cardiovascular diseases in three, infections in two, and other or unknown causes in three patients.

**Table 1.** Main characteristics of patients at the beginning of the study

	Number (%) of patients	Age, years	Late referral, n (%)	Causes of CKD, no				
				GN	PN	DN	HTA	Other
Men	24 (68.6%)	58.9 ± 15.27	7 (29.2%)	1	3	10	5	5
Women	11 (31.43%)	70.6 ± 13.27a	4 (36.4%)	0	1	1*	2*	7

CKD – chronic kidney disease; GN – glomerulonephritis; PN – pyelonephritis; DN – diabetic nephropathy; HTA – hypertension

Late referral - less than three months of follow-up by a nephrologist before the start of HD

\*significant difference in comparison to men

**Table 2.** Clinical characteristics and hemodialysis parameters of examined patients

		2014	2015	2016	2017	2018
No of patients	M	24	20	18	13	12
	W	11	10	8	5	5
BMI, kg/m <sup>2</sup>	M	26 ± 5.0	24 ± 9.2	n.a.	27 ± 4.6	26 ± 4.6
	W	23 ± 2.8*	23 ± 2.7*	n.a.	25 ± 1.8	24 ± 1.2
Systolic BP, mmHg	M	145.6 ± 14.6	141.6 ± 15.6	138.5 ± 14.6	138.1 ± 14.2	136.3 ± 12.2
	W	136.4 ± 15.3	135.4 ± 15.9	132.4 ± 13.8	131.4 ± 13.2	131.7 ± 12.9
Diastolic BP, mmHg	M	78.2 ± 12.4	77.5 ± 11.6	76.4 ± 11.2	76.8 ± 11.0	76.1 ± 11.3
	W	78.1 ± 13.4	76.2 ± 11.0	74.2 ± 10.5	74.4 ± 10.7	73.8 ± 11.0
Vascular access – AVF/CVC, no	M	8/16	18/2	17/1	13/0	12/0
	W	3/8	6/4	6/2	3/2	3/2
HD hours/week	M	11.1 ± 2.1	11.6 ± 2.0	11.6 ± 2.1	11.4 ± 1.9	11.4 ± 1.9
	W	11.1 ± 1.8	10.6 ± 1.6	10.6 ± 1.8	10.7 ± 1.7	10.7 ± 1.8
spKt/V	M	1.2 ± 0.3	1.1 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.3 ± 0.3
	W	1.3 ± 0.3	1.3 ± 0.3	1.4 ± 0.2*	1.4 ± 0.3	1.5 ± 0.3
ESA, no (%)	M	21 (87.5)	20 (100)	16 (88.9)	11 (84.6)	10 (76.9)
	W	9 (81.8)	8 (80.0)	7 (87.5)	4 (80.0)	3 (60.0)
Phosphate binders, no	M	23 (95.8)	19 (95)	18 (100)	11 (84.6)	11 (91.7)
	W	11(100)	10 (100)	8 (100)	4 (80.0)	5 (100)

M – men; W – women; BMI – body mass index, BP – blood pressure, AVF – arteriovenous fistula, CVC – central venous catheter, spKt/V – single-pool Kt / V, ESA – erythropoiesis stimulating agents; n.a. – not available

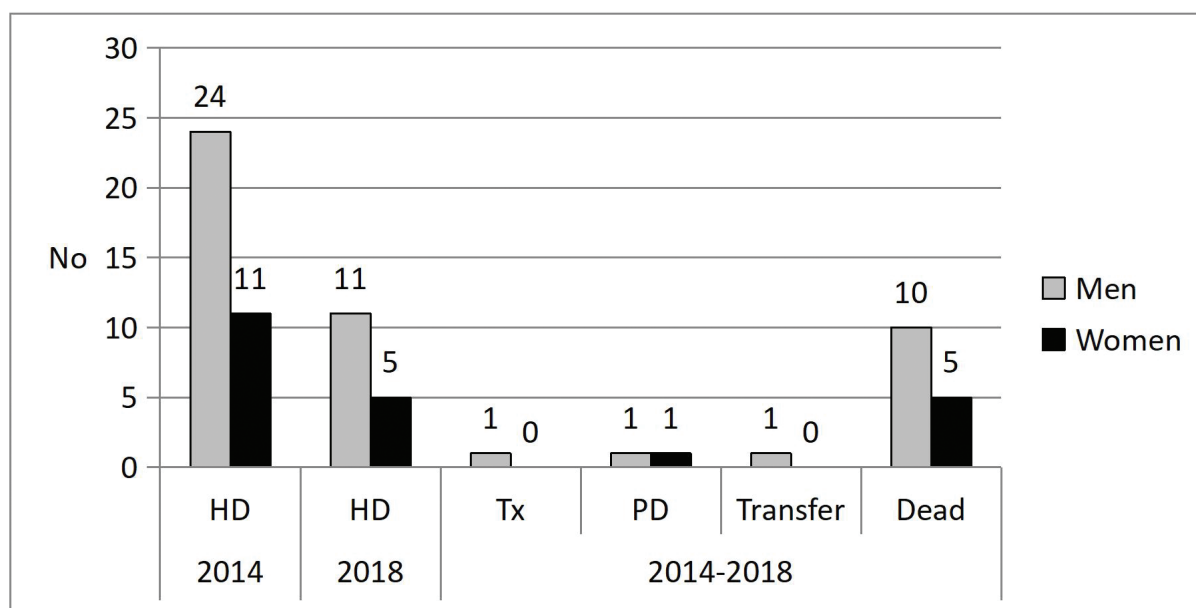
\*significant difference in comparison to men in that year

**Table 3.** Results of laboratory analyzes for examined patients during five-year study

	Sex	2014	2015	2016	2017	2018
Creatinine, $\mu\text{mol/L}$	M	765 $\pm$ 238	739 $\pm$ 210	710 $\pm$ 233	758 $\pm$ 212	816 $\pm$ 131
	W	693 $\pm$ 108*	674 $\pm$ 120	652 $\pm$ 165	832 $\pm$ 115	836 $\pm$ 158
Urea, mmol/L	M	21.4 $\pm$ 3.9	24.1 $\pm$ 6.2	21.6 $\pm$ 7.7	25.8 $\pm$ 6.2	24.5 $\pm$ 3.7
	W	25.1 $\pm$ 6.7	21.2 $\pm$ 4.2	25.1 $\pm$ 5.3	32.3 $\pm$ 3.4	23.7 $\pm$ 0.4
Calcium, mmol/L	M	2.4 $\pm$ 1.9	2.3 $\pm$ 0.2	2.2 $\pm$ 0.2	2.3 $\pm$ 0.3	2.3 $\pm$ 0.2
	W	2.4 $\pm$ 1.4	2.3 $\pm$ 0.2	2.2 $\pm$ 0.1	2.4 $\pm$ 0.4	2.4 $\pm$ 0.2
Phosphate, mmol/L	M	1.3 $\pm$ 0.3	1.6 $\pm$ 0.6	1.6 $\pm$ 0.6	1.5 $\pm$ 0.4	1.5 $\pm$ 0.5
	W	1.5 $\pm$ 0.5	1.7 $\pm$ 0.4	1.6 $\pm$ 0.6	1.5 $\pm$ 0.2	1.8 $\pm$ 0.4
iPTH, pg/mL	M	116.7 $\pm$ 73.8	127.9 $\pm$ 109.8	n.a.	139.2 $\pm$ 109.8	161.1 $\pm$ 99.4
	W	244.8 $\pm$ 100.9*	301.2 $\pm$ 122.1*	n.a.	184.2 $\pm$ 110.4*	176.6 $\pm$ 79.9
Hemoglobin, g/L	M	96 $\pm$ 14	112 $\pm$ 19	110 $\pm$ 16	104 $\pm$ 18	104 $\pm$ 16
	W	102 $\pm$ 16	117 $\pm$ 16	103 $\pm$ 19	108 $\pm$ 19	120 $\pm$ 18

M – men; W – women; n.a. – not available

\*significant difference in comparison to men in that year



**Figure 1.** Sex difference in the outcomes of examined patients

HD – hemodialysis; Tx – kidney transplantation; PD – peritoneal dialysis; Transfer – transfer to another center

## Discussion

The present retrospective longitudinal study was carried out to examine sex differences in patients starting regular HD in 2014 treated in two centers in southern Serbia, Leskovac and Pirot. The study involved 35 patients, 24 men and 11 women started HD treatment in 2014. At the beginning of the study women were significantly older, had significantly lower BMI and serum creatinine level than men, but diabetes and hypertension were significantly more frequent causes of CKD in men. Women had higher serum iPTH level in almost the entire study period in comparison to men. Although Kt/V was higher in women than in men during all five years, the differences were statistically significant only in the third year of the study. During all five years of the study there were no significant differences between men and women in blood pressure, type of vascular access, number of HD hours per week, the percentage of patients who used ESA or phosphate binders, as well as in hemoglobin and serum calcium and phosphate levels. In this period, 10/24 men and 5/11 women died and cerebrovascular diseases were the most frequent cause of death.

Although the prevalence of CKD is higher in women than in men, the percentage of women who start HD treatment is lower. The latest ERA-EDTA Registry Annual Report shows that in all European countries the percentage of men who started HD in 2019 was over 50%, being 56.8% in Iceland, 72.2% in Spain (Cantabria), and in Serbia 67.8% [4]. The question arises whether a smaller percentage of women start HD because their CKD progresses more slowly or there are barriers in women's access to HD [11]. Although in a recent interview nephrologists perceived that women with CKD faced many challenges in accessing care and HD [12], studies conducted so far have not confirmed that there is sex differences in HD access [13, 14]. Our study also did not show sex inequality in the

examined HD patients: similar percentages of patients of both sexes referred late to a nephrologist, there was no difference in vascular access, weekly HD hours, treatment with ESA and phosphate binders, as well as in patients' outcome.

The main objectives of the present study were to examine whether there were differences between men and women treated with HD and whether these differences changed over time. The results showed that both HD parameters and laboratory findings were similar in men and women ranging within the target values recommended by current KDIGO guidelines. As described by other authors [15], women had higher Kt/V than men during all five years, but in our study, most likely due to the small sample, the differences mostly did not reach statistical significance. Namely, when Kt/V is used as an index of dialysis adequacy in which V is urea distribution volume usually estimated from anthropometric equations, it may lead to overestimation of dialysis dose in women due to their smaller volume. Such approach can cause under-dialysis in women and requires caution [15, 16]. A smaller number of HD weekly hours for women in our study warns of this.

In the laboratory findings, there was only one significant difference between men and women: women had significantly higher serum iPTH level in almost the entire study period. It has been already described that female had an increased risk of parathyroid nodular hyperplasia and therefore higher serum iPTH level [17, 18]. This was explained by different factors, including the estrogen effect on parathyroid function as well as more common hyperphosphatemia in women [18].

We considered as important to compare the data on the sex differences in HD patients from our two centers from southern Serbia with data recently published for a larger group of HD patients from 28 HD centers in Serbia [19]. We noticed that women were significantly older at the beginning of treatment in our

centers compared to other centers. That can be explained, at least partly, by the faster progression of CKD in men included in our study who much more often had diabetes and hypertension as the underlying diseases. In contrast to the aforementioned study from Serbia, women dialyzed in our centers had the significantly higher serum iPTH level during all five years. Although this is in accordance with the results of other authors [17, 18], it obligates us to earlier and stricter prevention and treatment of hyperparathyroidism in women. The percentage of patients who died in our centers during five years was higher than the percentage described in the study from 28 centers in Serbia [19], especially for women, which was probably contributed to the significantly older age of the women in our centers. However, the causes of this difference in mortality require a more detailed analysis.

The present study has several limitations. The study included small number of patients from two HD centers and the results cannot be extended to the whole population of HD

patients in Serbia. Also, socio-economic factors were not analyzed although their impact was certainly significant.

## Conclusion

In two HD centers from southern Serbia, more than twice as many men than women started HD in 2014. The five-year retrospective study found the small number of differences between men and women. Higher Kt/V values in women should be interpreted with caution because this index overestimates the adequacy of HD in women. Higher serum level of iPTH in women suggests that prevention of hyperparathyroidism should begin in the early stage of CKD, especially in women, long before the kidney disease end stage. There were no differences in mortality and causes of death between men and women. Although the study revealed several differences between men and women on regular HD, no treatment inequality was found.

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**Ethical approval.** The Ethics Committee of the Leskovac General Hospital at the meeting held on February 15, 2019, approved the implementation of a retrospective

study. The decision was filed under number 330/2019. The research was conducted according to the Declaration of Helsinki.

**Conflicts of interest.** The authors declare no conflict of interest.

## References:

- Cobo G, Hecking M, Port FK, Exner I, Lindholm B, Stenvinkel P, Carrero JJ. Sex and gender differences in chronic kidney disease: progression to end-stage renal disease and haemodialysis. *Clin Sci (Lond)* 2016;130(14):1147–63.
- Žene i muškarci u Republici Srbiji. Beograd: Republički zavod za statistiku; 2020. Available from: <https://publikacije.stat.gov.rs/G2021/Pdf/G20216001.pdf>
- Carrero JJ, Hecking M, Chesnaye NC, Jager KJ. Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease. *Nat Rev Nephrol* 2018;14(13):151–64.
- ERA-EDTA Registry: ERA-EDTA Registry Annual Report 2019. Amsterdam UMC, location AMC, Department of Medical Informatics, Amsterdam, the Netherlands, 2021. Available from: <https://www.era-online.org/registry/AnnRep2019.pdf>
- Johansen KL, Chertow GM, Foley RN, Herzog CA, Ishani A, Israni AK, Ku, et al. US Renal Data System 2020 Annual Data Report: epidemiology of kidney disease in the United States. *Am J Kidney Dis* 2021;77(4 Suppl 1):A7–A8.
- Godišnji izveštaj Udruženja nefrologa Srbije, 2014. Beograd: Udruženje nefrologa Srbije; 2016. Available from: <https://www.udruzenjenefrologa.com/download/godisnji-izvestaj-o-lecenju-dijalizom-i-transplantacijom-bubrega-u-srbiji-2014/?wpdmdl=4775&refresh=62a999068ba451655281926>
- Carrero JJ, Hecking M, Chesnaye NC, Jager KJ. Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease. *Nat Rev Nephrol* 2018;14(3):151–64.
- Shah S, Leonard AC, Meganathan K, Christianson AL, Thakar CV. Gender and racial disparities in initial hemodialysis access and outcomes in incident end-stage renal disease patients. *Am J Nephrol* 2018;48(1):4–14.
- Tong A, Evangelidis N, Kurnikowski A, Lewandowski M, Bretschneider P, Oberbauer R, et al. Nephrologists' Perspectives on Gender Disparities in CKD and Dialysis. *Kidney Int Rep* 2021;7(3):424–35
- Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. *J Am Soc Nephrol* 1993;4(5):1205–13.
- Fernandez-Prado R, Fernandez-Fernandez B, Ortiz A. Women and renal replacement therapy in Europe: lower incidence, equal access to transplantation, longer survival than men. *Clin Kidney J* 2018;11(1):1–6.
- Tong A, Evangelidis N, Kurnikowski A, Lewandowski M, Bretschneider P, Oberbauer R, et al. Nephrologists' Perspectives on Gender Disparities in CKD and Dialysis. *Kidney Int Reports* 2021;7(3):424–35.
- Kainz A, Berner C, Ristl R, Simon A, Stamm T, Zitt E, et al. Sex-specific analysis of haemodialysis prevalence, practices and mortality over time: the Austrian Dialysis Registry from 1965 to 2014. *Nephrol Dial Transplant* 2019;34(6):1026–35.
- Weigert A, Drozd M, Silva, Frazão J, Alsuwaida A, Krishnan M, et al. Influence of gender and age on haemodialysis practices: a European multicentre analysis. *Clin Kidney J* 2020;13(2):217–24.
- Spalding EM, Chandna SM, Davenport A, Farrington K. Kt/V underestimates the hemodialysis dose in women and small men. *Kidney Int* 2008;74(3):348–55.
- Perez-Garcia R, Jaldo M, Alcazar R, de Sequera P, Alvalate M, Puerta M, et al. Unlike Kt, high Kt/V is associated with greater mortality: The importance of low V. *Nefrologia (Engl. Ed)* 2019;39(1):58–66.
- Cheng S-P, Yang T-L, Lee J-J, Chen H-H, Wu C-J, Liu T-P, et al. Gender Differences Among Patients with Secondary Hyperparathyroidism Undergoing Parathyroidectomy. *J Surg Res* 2011;168(1):82–7.
- Bures C, Skachko T, Dobrindt EM, Pratschke J, Uluk S, Mogl MT. Is There a Gender Difference in Clinical Presentation of Renal Hyperparathyroidism and Outcome after Parathyroidectomy? *Visc Med* 2020;36(1):34–40.
- Djukanović L, Ležaić V, Dimković N, Marinković J, Aksić Milićević B, Arsenijević S, et al. Gender-specific differences in hemodialysis patients: a multicenter longitudinal study from Serbia. *Int Urol Nephrol* 2022;54(12):3233–42.

## Razlike zavisne od pola kod bolesnika lečenih redovnim hemodijalizama

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**Uvod.** Cilj studije je bio da se utvrde razlike među polovima kod bolesnika koji su lečenje hemodijalizom (HD) započeli 2014. godine i proveri da li se te razlike menjaju tokom petogodišnje studije.

**Metode.** Retrospektivna petogodišnja studija obuhvatila je 35 bolesnika (24 muškarca i 11 žena) koji su započeli lečenje HD u centrima za HD u Leskovcu i Pirotu 2014. godine. Demografski i klinički podaci, laboratorijski nalazi, podaci o lekovima koje su bolesnici koristili dobijeni su iz medicinske dokumentacije.

**Rezultati.** Poređenje bolesnika različitog pola na početku studije je pokazalo da su žene bile značajno starije ( $70,55 \pm 13,27$  vs.  $58,88 \pm 15,27$  godina), a dijabetes i hipertenzija značajno češći uzroci hronične bolesti bubrega kod muškaraca. Žene su imale značajno manji indeks telesne mase i koncentraciju kreatinina u serumu nego muškarci u prvoj godini studije. Tokom pet godina indeks adekvatnosti HD spKt/V je bio veći kod žena nego kod muškaraca, ali je razlika bila značajna samo u trećoj godini ( $1,4 \pm 0,2$  vs.  $1,2 \pm 0,2$ ). Koncentracija iPTH u serumu je bila veća kod žena nego kod muškaraca gotovo tokom celog petogodišnjeg perioda. Nije bilo značajne razlike među polovima u visini krvnog pritiska, tipu vaskularnog pristupa, nedeljnom broju časova HD, procentu bolesnika koji su lečeni agensima za stimulaciju eritropoeze ili vezačima fosfata. Tokom studije 10 (42,7%) muškaraca i 5 (45,5%) žena je umrlo, a najčešći uzrok smrti su bile cerebrovaskularne i kardiovaskularne bolesti.

**Zaključak.** Studija je otkrila nekoliko razlika između muškaraca i žena na redovnim HD, ali ne i nejednakost u lečenju.

**Ključne reči:** bolesnici na hemodijalizi, razlike među polovima, retrospektivna studija