

TREND OF KIDNEY REPLACEMENT THERAPY IN NORTH MACEDONIA FROM THE YEARS 2015 THROUGH 2020

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ABSTRACT

Introduction: Kidney replacement therapy (KRT) by dialysis or kidney transplantation represents the main treatment modalities for patients with kidney failure. Here we evaluate the trends in taking care of such patients in North Macedonia from 2015 through 2020.

Methods: The patients were analyzed according to age, sex, primary disease, and treatment modality. They were further subdivided into 3 groups: Group 1, prevalent patients; Group 2, incident patients with analysis starting at day 1 of KRT; and Group 3, incident patients with analysis starting at day 91 of KRT.

Results: The study included 10,395 person-years, mean age 59.2 ± 9.5 years, male sex 60.2%, hemodialysis therapy 84.7% in 2015 and 85.9% in 2020. Hypertension and diabetes mellitus were the leading causes of kidney disease. Group 1 showed an increase in KRT care of 10.3% (from 799 part per million population [pmp] in 2015 to 881 pmp in 2020). In Group 2 the number of patients was increasing with each successive year, the highest growth being observed in 2019. The patients of Group 3 showed a significant growth during this time period, from 126.5 ppm in 2015 to 162 pmp in 2019, but a subsequent decrease of 16.4% in 2020 (135.5 pmp), probably explained by the SARS-CoV-2 pandemic.

Conclusion: In the analyzed period, an increase in the number of patients with kidney failure in need of KRT is observed. We believe that this trend will continue in the following years, which should be taken into account when planning health policies in our country in the future.

Keywords: kidney failure, dialyze, transplantation, hypertension, diabetes mellitus

INTRODUCTION

Chronic kidney disease (CKD) is a progressive and irreversible damage of the kidney tissue characterized by a reduction in estimated glomerular filtration rate (eGFR) and/or proteinuria [1, 2]. It is a global public health issue associated with a huge economic burden on healthcare systems worldwide [3]. The current estimates show that CKD affects > 10 % of the general population worldwide, accounting for > 800 million individuals [4]. In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group reported an updated nomenclature of CKD, defining the disease as a structural or functional abnormality of the kidney for at least 3 months, manifested by kidney damage (often presented with albuminuria) with or without reduced eGFR to a value <60 mL/min/1.73m², or a decreased eGFR with or without other evidence of kidney damage for at least 3 months. The new classification system incorporates a three-dimension operational definition for CKD that includes cause, eGFR category, and albuminuria category (CGA). The treatment of CKD can be conservative (patients without indication for dialysis, usually those with eGFR above 15 mL/min/1.73m²) or with kidney replacement therapy (KRT) [5].

At present, about 2 to 3 million people require KRT, and the prevalence is constantly increasing by 1-2% per year. The annual reports of the European Renal Association (ERA) registry show the incidence and prevalence of the patients who need KRT by age, sex, primary renal disease, factors related to the progression of CKD, survival from competing risks like cardiovascular disease (CVD), vascular access, and the timing of KRT initiation in relation to eGFR. To date, the incidence of KRT remains relatively stable in high-income countries, while it progressively increases in middle-income and also several low-income countries. The prevalence of KRT increases globally [7]. This is likely due to increased survival, demographic shifts, the increased prevalence of risk factors for CKD, and better access to health care [7, 8].

North Macedonia (N. Macedonia) is among the countries with medium-high income according to economic development, and progress has been made in the economic and medical sectors in the last decade [9]. Based on this favorable evolution, we aimed to evaluate whether such progress

is also reflected in the incidence of KRT in our country. Specifically, we analyzed the trends of KRT in N. Macedonia in the six-year period from 2015–2020.

METHODS

The study was observational and retrospective, including 10.395 person-years with end stage kidney diseases (ESKD) who initiated KRT in the time period of 2015-2020. The data were processed from the annual ERA reports. They were analyzed by year of KRT start, and aggregated into three groups of patients. Group 1 (prevalent) are KRT patients of the current year, Group 2 (incident 1) KRT patients with a duration of at least 1 day, and Group 3 (incident 91) KRT patients with continued treatment beyond 91 days. The number of patients was presented as per million population (pmp). We assume that the total population of N. Macedonia approximates 2 million, and this is the denominator used throughout the analyses.

The epidemiological data of all patients were analyzed including age, sex, primary renal disease, and modality of KRT. Available information on primary renal disease was categorized into eight groups: hypertension, diabetes mellitus, pyelonephritis, glomerulonephritis, polycystic kidney disease, renovascular disease, miscellaneous, and unknown. We used the Mann-Whitney U test as the non-parametric alternative test to compare prevalence and incidence (1 and 91) during the observation period. Differences and absolute counts regarding age group, sex, mode of KRT, and reported primary renal disease were described for each subsequent year and each patient group, allowing comparisons of each year with the previous year.

RESULTS

Patient data were collected from 23 hemodialysis centers and a kidney transplantation center for the Renal Registry of N. Macedonia which is part of the Nationality registers of the ERA. Patients mean age was 59.2 ± 9.5 years (median 60.4 years), with 60.2% males. (Table 1) Half of the patients (50%) were in age group 45-64 years (Table 2), and HD was the main

Table 1. *Patients on KRT by year and gender, 2015 – 2020*

Year	Registered patients	Totals pmp	Calculated 95 % CI	% Change from the previous year	% male patients	%, female patients
2015	Prevalent patients	799	[797 – 800]	0 %	58.1 %	41.9 %
2016		832.5	[825 – 827]	4.2 %	59.4 %	40.6 %
2017		880.5	[879 – 881]	5.8 %	59.5 %	40.5 %
2018		878	[876 – 879]	-0.3 %	60.4 %	39.6 %
2019		926.5	[925 – 927]	5.5 %	60.1 %	39.9 %
2020		881	[879 – 823]	-4.9 %	61.6 %	38.4 %
2015	Incident patients on KRT at Day 1	153.5	[153 – 154]	0 %	56 %	44 %
2016		166	[165 – 166]	8.1 %	61.4 %	38.6 %
2017		182.5	[182 – 183]	9.9 %	57.8 %	42.2 %
2018		169.5	[169 – 170]	-7.1 %	62.5 %	37.5 %
2019		190	[189 – 191]	12.1 %	60.0 %	40 %
2020		190.5	[190 – 191]	0.3 %	61.7 %	38.3 %
2015	Incident patients on KRT at Day 91	126.5	[126 – 127]	0 %	56.5 %	43.5 %
2016		132.5	[132 – 133]	4.7%	62.6 %	37.4 %
2017		138.5	[138 – 139]	4.5%	58.1 %	41.9 %
2018		139.5	[139 – 140]	0.7%	63.8 %	36.2 %
2019		162	[161 – 163]	16.1%	60.5 %	39.5 %
2020		135.5	[135 – 136]	-16.4%	64.2 %	35.8 %

*KRT- kidney replacement therapy

Table 2. *Age structure of patients on KRT, 2015–2020*

Year	Age group	0 - 19 years	20-44 years	45-64 years	65-74 years	75 years or more
2015	Prevalent patients	0.6 %	16.6 %	49.4 %	21.5 %	11.9 %
2016		0.6 %	14.9 %	49.4 %	22 %	13.2 %
2017		0.5 %	14.5 %	48.4 %	22.5 %	14.1 %
2018		0.7 %	14.6 %	48.4 %	23.1 %	13.3 %
2019		0.4 %	13.2 %	45.8 %	26.4 %	14.1 %
2020		0.6 %	13.5 %	46.3 %	25.4 %	14.2 %
2015	Incident patients at Day 1	0.8 %	9.9 %	40.7 %	29.2 %	19.4 %
2016		0.8 %	8.7 %	44.2 %	27.2 %	19.2 %
2017		0.7 %	11.6 %	45.5 %	22 %	20.2 %
2018		1.4 %	11.1 %	43.4 %	25.8 %	18.3 %
2019		0 %	5.6 %	40.7 %	35.2 %	18.5 %
2020		1.8 %	9.2 %	40.2 %	28.4 %	20.3 %
2015	Incident patients at Day 91	0.7 %	8.1 %	37.8 %	30.3 %	23.1 %
2016		0.6 %	8.1 %	40.4 %	28.9 %	22 %
2017		0.5 %	9.9 %	40.8 %	26.3 %	22.5 %
2018		1.2 %	9.7 %	39.2 %	25.7 %	24.2 %
2019		0 %	5.5 %	37.6 %	35 %	21.8 %
2020		1.3 %	7.9 %	36.7 %	30.7 %	23.4 %

treatment modality (84.7% in 2015 and 85.9% in 2020). (Figure 1) Hypertension and diabetes mellitus were the leading causes of primary renal disease. (Table 3) There was a slight annual increase in the number of patients in all groups in the time period 2015 - 2020. Group 1 (prevalent) exhibited 799 pmp patients in year 2015, with an increase of 10.3% in year 2020 (881 pmp). The number of patients in Group 2 (incident 1) increased every year, with the highest increase in year 2019 (12.1% compared to the previous year). (Table 1) In Group 3 (incident 91) the number of patients increased from 126.5 pmp in 2015 to 162 pmp in 2019, although it subsequently decreased by 16.4% (135 pmp) in 2020. This deviation from then increasing trend in the preceding years, with a decrease in the number of patients in Group 1 (prevalent) and Group 3 (incident 91), as well as a slow-down in the growth dynamics of patients in Group 2 (incident 1) corresponds to the early time period of the SARS-CoV-2 pandemic. (Table 1)

In addition, the U test showed a significant value of $p < .05$ between prevalence and incidence (day 1 and day 91) during the evaluation period [U value 1.5; the critical value of U $p < .05$ is 5; z-score is 2.56205 with $p .01046$].

As regards age distribution, the majority of patients were aged 45 to 64 (36.3% to 49.4%) across all 3 groups, followed by patients aged 65 to 74. (Table 2) Furthermore, an increase was observed in the prevalence of patients aged above 75 in Group 1, starting from 11.9% in 2015 to 14.2% in 2020. A similar increase was observed in the incidence of patients aged above 75 in Group 2 (incident 1) and Group 3 (incident 91), indicating a long-term trend towards this age group. It is also worth noting that 24.2% of all patients in 2018 were aged 75 years or older. (Table 2)

As to the sex of the registered patients, the number of male patients slightly increased in all groups from 2015 to 2020. Specifically, the prevalence of males in Group 1 showed a consistent growth from 58.1% in 2015 to 61.6% in 2020. (Table 1)

The analysis of primary renal diseases showed a predominance of hypertension and diabetes mellitus in all groups. (Table 3) The prevalence of hypertension in Group 1 increased from 194 pmp (24.3%) in 2015 to 236 pmp (26.8%) of all reported etiologies in 2020. Diabetes mellitus was reported as the underlying cause in 15.3% and 17.7% of all Group 1 patients for 2015 and

Table 3. Primary renal diseases in patients on KRT, 2015 - 2020

Year	Etiological group	Miscellaneous	Unknown	Diabetes mellitus	Arterial hypertension	Glomerulo-nephritis	Pyelo-nephritis	Polycystic kidney disease	Reno-vascular
2015	Total proportion of prevalent patients	13.5%	12.7%	15.3%	24.3%	15.9%	7.9%	10.3%	0.1%
2016		9.3%	12.9%	16.4%	24.9%	17.4%	9.1%	9.8%	0.2%
2017		8.1%	14.1%	17.0%	25.3%	16.9%	9.1%	9.4%	0.1%
2018		8.2%	13.1%	17.3%	25.9%	16.8%	9.6%	8.9%	0.2%
2019		9.9%	12.8%	17.8%	26.1%	15.3%	7.6%	9.5%	1.0%
2020		9.7%	14.0%	17.7%	26.8%	14.9%	7.1%	9.5%	0.3%
2015	Incident patients at Day 1	16.6%	12.1%	23.1%	28.3%	7.2%	5.2%	7.2%	0.3%
2016		11.7%	16.9%	25.3%	25.6%	8.7%	6.3%	5.5%	0.0%
2017		12.3%	12.3%	27.4%	27.4%	9.0%	6.1%	5.5%	0.0%
2018		8.3%	14.5%	30.6%	24.5%	8.3%	9.1%	4.1%	0.6%
2019		11.3%	20.3%	24.7%	25.0%	5.8%	5.0%	5.3%	2.6%
2020		11.0%	16.8%	25.2%	31.2%	4.2%	7.1%	4.0%	0.5%
2015	Incident patients at Day 91	16.2%	9.5%	24.1%	28.9%	8.3%	4.3%	8.3%	0.4%
2016		8.4%	16.6%	24.9%	28.3%	9.4%	6.4%	6.0%	0.0%
2017		5.8%	14.1%	24.9%	31.0%	10.1%	6.9%	7.2%	0.0%
2018		8.7%	11.8%	30.8%	25.8%	10.0%	7.5%	5.0%	0.4%
2019		11.7%	16.0%	26.9%	26.5%	6.3%	5.2%	5.9%	1.5%
2020		11.1%	16.2%	23.6%	32.8%	4.5%	5.9%	5.2%	0.7%

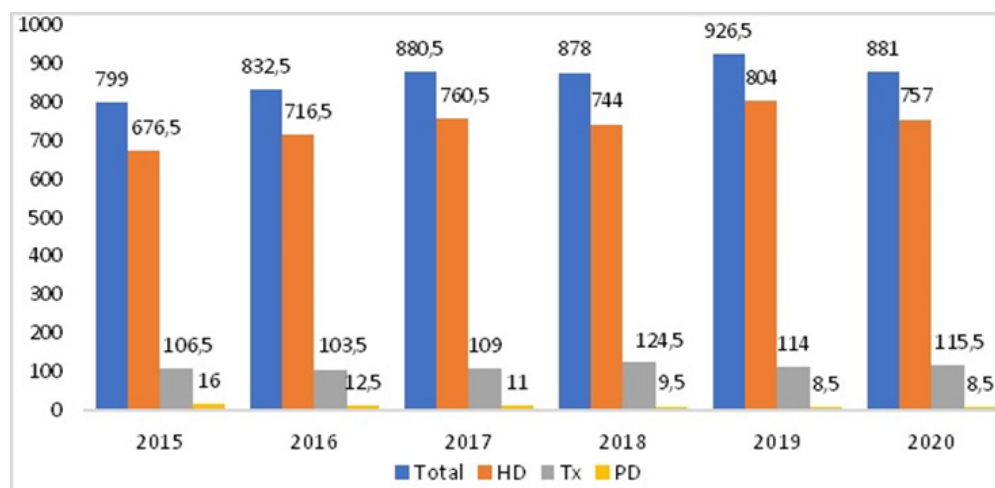


Figure 1. Total number of patients (pmp) on KRT, 2015–2020

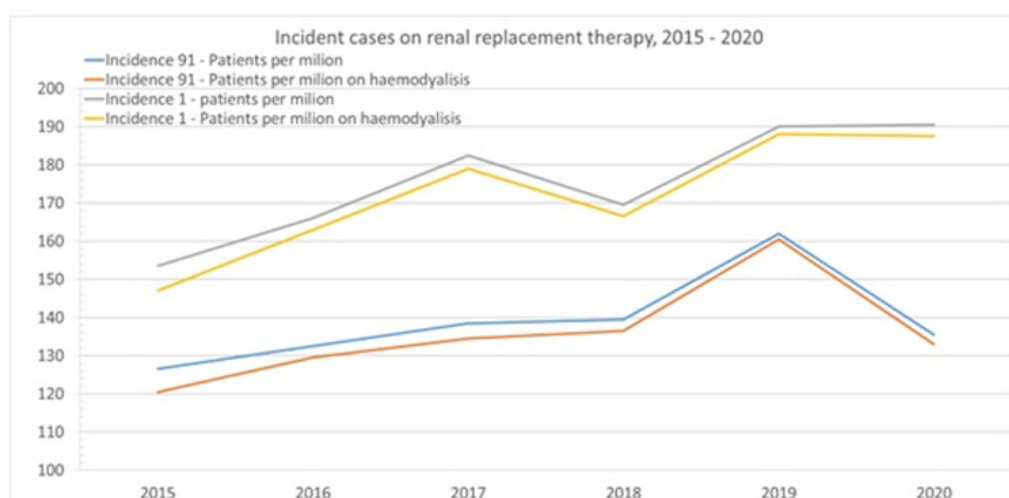


Figure 2. Incident cases on KRT; 2015–2020

2020, respectively. This finding applied to all groups for the entire time period, with hypertension and diabetes mellitus being reported as etiologic diagnoses of kidney failure in more than 40% of the patients. An additional finding is the increase in all groups of cases developing kidney failure in the years 2019 and 2020 where renovascular was reported as the cause of CKD (compared to the preceding years). The number of patients with unknown etiology increased as well, with a higher representation in Group 2 (incident 1). (Table 3) Although the proportion of cases with unknown etiology increased during this period, the total number of patients reaching ESKD did not change due to a decrease in the proportion of cases with miscellaneous etiology.

As regards the modality of KRT, hemodialysis was the main treatment modality in all groups and years. In Group 1 (prevalent) patients HD initiation first increased from 676.5 pmp in

2015 to 804 pmp in 2019, but decreased subsequently to 757 pmp in 2020. The number of patients receiving peritoneal dialysis (PD) therapy was halved during this time period, from 16 pmp in 2015 to 8.5 pmp in 2020. The number of patients who received a kidney transplant increased moderately, from 106.5 pmp in 2015 to 124.5 pmp in 2018, followed by a decline to 115.5 pmp in 2020. (Figure 1)

DISCUSSION

The main finding of our study is that a growing number of patients in N. Macedonia started KRT in the time period of 2015 through 2020. Overall, the KRT prevalence increased by 10.3%, predominantly reflecting an increase in the age group of 65 years or more (3.9% in age

group 65-74 years, and 2.2% in age group >75 years). Over the years, the rate of increase in other age groups did not change (patients < 19 years) or slightly declined in the age groups 20-44 and 45-64 years. However, the average prevalence in our study was 866.25 ± 1.2 (CI 95%; 865.04-867.46). Similar results were obtained for N. Macedonia in the period 2002-2007. This was also reflected by a gradual, continuous increase in KRT prevalence over the years [10].

According to 2019 Global Kidney Health Atlas (GKHA) cross-sectional survey of the International Society of Nephrology (ISN) in 91 participating countries the average prevalence of people receiving KRT globally was 759 pmp. Taiwan had the highest prevalence of 3.392 pmp, followed by Japan (2.599 pmp) and the USA (2.196 pmp). The lowest prevalence (117-540 pmp) was reported by Bangladesh, South Africa, Ukraine, Belarus, Iraq, Russia, Indonesia, Guatemala, Albania, Peru, Latvia, Serbia, and Bulgaria.11 In our country, the average prevalence was slightly above the world average, with 799 pmp in 2015 and 881 pmp in 2020.

The present study showed a parallel increase in the number of incident patients on KRT in Group 2 (incident 1) and Group 3 (incident 91). Our analysis reported that average (incident 1) was $175.33 \text{ pmp} \pm 0.89$ (CI 95%; 174.43-176.22), and average (incident 91) was $139.08 \text{ pmp} \pm 0.83$ (CI 95%; 138.25 - 139.91). Also, the average global incidence of patients with KF treated with KRT is 144 pmp and varied greatly across countries (from 378 pmp in the USA to 85 pmp in Albania and Estonia) in 2016 [11]. The incidence of treated ESKD in high-income countries from 2003 to 2016 (European countries, Australia, New Zealand, Japan, and the USA) remained relatively stable in contrast to some East and Southeast Asian countries where the incidence rates increased substantially [11]. According to our previous study, the incident counts on KRT pmp at Day 1 and 91 showed the same continuous gradual increase over the years [10]. It is believed that rising ESKD prevalence and incidence worldwide was due to improved survival, aging of the world population with rising prevalence of diabetes mellitus, hypertension, and obesity in association with urbanization and changes in diet and physical activity, and improved access to KRT in countries with growing economies [11,12]. In line with our findings and the establishment of the ERA Registry, few-

er women than men received KRT. The reasons for these observations are unclear. It might be explained to a certain extent by the slower progression towards kidney failure among women with CKD due to hormonal protection before menopause, differences in oxidative stress, improved lifestyle, and better treatment compliance [12,13].

In 2020, we observed a decrease in the number of patients in Group 1 (prevalent) and Group 3 (incident 91) and a slowdown in growth dynamics in Group 2 (incident 1), corresponding to the early phase of the SARS-CoV-2 pandemic. In this year, although the incident cases on KRT with a duration of less than 91 days (Incident 1) remained stable, the number of patients on KRT beyond 91 days dropped by 1.3%. (Figure 2) The drop might be explained by the higher mortality rate of these patients in the SARS CoV-2 pandemic, as noted in many other studies [14-16]. In terms of the primary renal disease, hypertension, and diabetes mellitus were the predominant etiologies in all patient groups in our cohort. The percentage of prevalent patients with hypertension and diabetes mellitus showed a continuous upward trend from 2015 to 2020. Diabetes mellitus and hypertension were also the most frequent etiologies among incident patients. Among Group 2 (incident 1) the average percentage of patients with unknown renal failure was 14.03%, followed by an upward trend over the years with a particular increase in year 2020 that could be partially explained by the start of the SARS-CoV-2 pandemic, with a reduced number of renal biopsies. According to the 2020 ERA registry, diabetes mellitus was the most common primary renal disease, encountered in 21% of incident patients and 15% of prevalent patients. There was a decrease in the percentage of incident and prevalent patients with diabetes mellitus compared to 2015 (2% and 1%, respectively). Hypertension was diagnosed in 10% of prevalent patients, that is half that of our results [17]. However, the majority of our patients with hypertension had no kidney biopsy, therefore the prevalence of hypertension was probably overestimated. Wakasugi et al. reported that in Japan, the number of incident patients on KRT due to chronic glomerulonephritis and diabetes mellitus decreased from 2006 to 2020, while the number of incident patients on KRT ascribed to hypertension increased by 3.3% and 1.4% per year for men and women, respectively [18]. In contrast, Stel et al. found the percentage of inci-

dent patients on KRT with diabetes mellitus and hypertension to remain unchanged, with slight variations in high-income countries, although these two etiologies exhibited an ever-increasing cause of kidney failure in many low and middle-income countries [19].

In our cohort, in-center hemodialysis was the most frequent KRT modality in all patient groups. Its prevalence had a continuous upward trend from 2015 to 2019, though with a slight decrease in 2020 probably related to the SARS-CoV-2 pandemic. Such a negative effect of the SARS-CoV-2 pandemic was also reported by Jager et al. who also observed an increase in mortality risk of older patients with KRT, more so in men than in women, and in kidney transplant recipients compared with matched dialysis patients [16]. Clearly, patients who require KRT represent a highly vulnerable population due to CKD and a high prevalence of multiple comorbidities [16].

Worldwide HD is the most common KRT modality, with more than 80% of chronic dialysis patients receiving in-center HD [20]. Peritoneal dialysis was the preferred treatment modality of ESKD in Hong Kong, Mexico, and Guatemala, used by more than two-thirds of their patients [11]. This is also true in Europe where in 2020, 58% (538 pmp) of prevalent ESKD patients were treated with HD, and only 5% (45 pmp) with PD [17]. The predominance of in-center HD in our country can be explained by a highly developed network of centers that provide HD treatment closes to each patient's place of residence, and by the yet insufficient availability of kidney transplantation. In 2020 only 11.8% of all ESKD patients in our country received a kidney graft, which is three times less compared to the European average published in the 2020 ERA Registry [16]. PD is also poorly developed in N. Macedonia, being usually reserved as a very last resource for patients with exhausted vascular access possibilities.

Achieving global equity in patients who need KRT will require concerted efforts in advocating effective public policy, health care delivery, workforce capacity, education, research, and support from the government, private sector, and nongovernmental as well as professional organizations. The main strength of our study is the continuous monitoring of all patients in need of KRT among the population of 2 million inhabitants in N. Macedonia, as initiated in 2002 [10].

We hope that the results of the present analysis will help planning future healthcare policies in our country. We analyzed more than 10,000 person-years grouped into multiple categories and proceeded to appropriate comparisons with other countries wherever possible. In accordance with world trends and the present statistical analysis, our prediction is to achieve 1000 pmp prevalent patients with KRT by 2030 in N. Macedonia.

Study limitations are that the analysis covers a time period of only 6 years, with the risk of providing an incomplete long-term insight into the real situation. The 2020 data were heavily impacted by the SARS-CoV-2 pandemic and related to work in emergency conditions. Moreover, insufficient information was available about patient survival during the analysis period. However, this should not have affected the final conclusions of the study.

CONCLUSION

We note a continuous increase in the prevalence and incidence of patients with ESKD and of KRT from 2015 to 2020. The majority of patients were aged between 45-64 years, followed by patients aged 65 or more years. The incidence and prevalence of KRT were consistently higher in male than female patients. As expected, diabetes mellitus and hypertension were the leading causes of kidney failure. Finally, HD was the main treatment modality in N. Macedonia.

Abbreviations:

CKD	– Chronic kidney disease
eGFR	– Estimated Glomerular filtration rate
ERA	– European Renal Association
NKF-KDOQI	– National Kidney Foundation-Kidney Disease Outcomes Quality Initiative
ESKD	– End-stage kidney disease
HD	– Hemodialysis
KRT	– Kidney replacement therapy
KF	– Kidney failure
PD	– Peritoneal dialysis
Tx	– Kidney transplantation
CVD	– Cardiovascular disease
pmp	– per million population

ISN – International Society of Nephrology's

GKHA – Global Kidney Health Atlas

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Резиме

ТРЕНД НА БУБРЕЖНО ЗАМЕСТИТЕЛНАТА ТЕРАПИЈА ВО СЕВЕРНА МАКЕДОНИЈА ВО ПЕРИОДОТ ОД 2015 ДО 2020 ГОДИНА

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Вовед: Бубрежно заместителната терапија (БЗТ) во облик на дијализа или на бубрежна трансплантација претставува главен терапевтски модалитет за лекување на пациентите со терминална бубрежна слабост. Во овој ракопис ние ги евалуираме состојбите и модалитетите за третман на овие пациенти во РС Македонија во периодот од 2015 до 2020 година.

Материјали и методи: Пациентите беа анализирани според возраста, полот, основната бубрежна болест и применетиот облик на лекување. Беа поделени во три подгрупи: Група 1 (превалентни пациенти), Група 2 (инцидентни пациенти анализирани на првиот ден од отпочнување со БЗТ) и Група 3 (инцидентни пациенти анализирани на 91 ден од отпочнување со БЗТ).

Резултати: Студијата вклучуваше анализа на 10,395 лица-години (person-years), со средна возраст $59,2 \pm 9,5$ години, 60,2 % беа мажи, а застапеноста на лекување со хемодијализа беше 84,7 % во 2015 година и 85,9 % во 2020 година. Хипертензијата и дијабетот беа водечки причини за бубрежна слабост. Групата 1 покажа зголемување на бројот на пациенти со БЗТ за 10,3 % (од 799 пациенти на милион популација во 2015 година на 881 пациенти на милион популација). Во Групата 2 бројот на пациенти растеше секоја година, а највисок раст беше забележан во 2019 година. Бројот на пациенти во Групата 3 исто така покажа значителен раст во текот на анализираниот период, од 126,5 пациенти на милион популација во 2015 година на 162 пациенти на милион популација во 2019 година, со намалување од 16,4 % во 2020 година (135,5 пациенти на милион популација), веројатно поради пандемијата со вирусот САРС КоВ-2.

Заклучок: Во анализираниот период се забележува зголемување на бројот на пациентите со бубрежна слабост со потреба од БЗТ. Веруваме дека ваквиот тренд ќе продолжи и во следните години, што треба да се земе предвид при планирањето на здравствените политики во нашата земја во иднина.

Клучни зборови: бубрежна слабост, дијализа, бубрежна трансплантација, хипертензија, дијабетес мелитус

