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CLINICAL STUDY

# How COVID-19 crisis influenced kidney transplant recipients in Slovakia

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**ABSTRACT**

OBJECTIVES: The aim of our analysis was to evaluate the impact of the COVID-19 pandemic on the procurement program and kidney transplantation in Slovakia and to identify the risk factors for a severe course of COVID-19 disease, as well as the risk factors for COVID-19 fatalities, with the focus on the parameters preceding the infection. We compared morbidity and mortality from COVID-19 before and after the spread of the alpha variant of the virus and the same among transplant (KTRs) and haemodialysis patients in Slovakia.

METHODS: 305 KTRs (68.8 % males) with confirmed SARS-CoV-2 positivity were included in the multicentric retrospective analysis. The patients were split into subgroups based on the time of falling ill and their clinical course.

RESULTS: The procurement program and kidney transplants in Slovakia dropped in the observed period by 28.6 % ($p<0.0001$) and by 33.5 % ($p<0.0001$) respectively. Age over 59 years ($p=0.0088$) and diabetes mellitus ($p=0.0106$) were identified as independent risk factors for severe course of the disease. Risk factors for death were the age over 59 years ($p=0.0003$) and graft dysfunction with CKD-EPI<0.5 mL/s ($p=0.0029$). The prevalence of the alpha variant in Slovakia was associated with a severe course in KTRs treated with corticoids ($p=0.0273$) and in graft dysfunction with CKD-EPI<0.5 mL/s ($p=0.0076$); the risk of death was higher in KTRs over 59 years ($p=0.0173$) and again with CKD-EPI<0.5 mL/s ($p=0.0393$). KTRs had a 3.7 times lower risk of infection compared to the haemodialysis patients ($p<0.0001$), with mortality of 9.8 % *vs* 30 % ($p<0.0001$).

CONCLUSION: The procurement and transplant program is sustainable even during a pandemic, provided that measures are set up quickly. Morbidity and mortality from COVID-19 in KTRs was comparable to the situation in EU countries. Patients in the haemodialysis program had a worse prognosis *(Tab. 5, Fig. 1, Ref. 21)*. Text in PDF *www.elis.sk*

KEY WORDS: COVID-19, kidney transplantation, dialysis, immunosuppression, obesity, diabetes mellitus.

**Abbreviations:** ACE-I – angiotensin-converting enzyme inhibitor, BMI – body mass index , CKD – chronic kidney disease, CKD-EPI – chronic kidney disease epidemiology collaboration, COVID-19 – coronavirus disease 2019, CNI – calcineurin inhibitor, DBD – donation after brain death, ERACODA – the European Renal Association COVID-19 Database , ERA-EDTA – the European Renal Association, EuClid5 – Nephrocare European Clinical Database, EU – European Union, eGFR – estimated glomerular filtration rate, HD – hemodialysis, IV – intravenously, KTRs – kidney transplant recipients, LKD – living kidney donor, MMF – mycophenolate mofetil, MPA – mycophenolic acid , mTOR –I, inhibitor of mammalian target of rapamycine, RT PCR – real-time polymerase chain reaction, SARS-CoV-2 – severe acute respiratory syndrome coronavirus-2, TAC – tacrolimus , *Vs* – versus

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## Introduction

Since the initial outbreak in Wuhan, China, in December 2019, the Coronavirus Disease 2019 (COVID-19) has spread across the world, prompting a global pandemic. The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was seen as a pulmonary and infectious problem (1).

The other conditions initially identified as risk factors for a severe course of COVID-19 were cardiovascular disease, diabetes,

and hypertension. Only later in the process came the realization that kidney disease is the leading risk factor for death. Ultimately, it appeared that the population of the patients with chronic kidney disease (CKD), especially those treated with dialysis or transplantation, is one of the highest-risk groups for hospitalization and death (2, 3, 4). Dialysis and transplant patients represent a vulnerable population as all of them suffer from multiple pre-existing medical conditions. COVID-19 causes a substantial mortality in both dialysis and kidney transplant population due to their underlying chronic kidney disease and a high prevalence of comorbid conditions such as: hypertension, diabetes mellitus, and cardiovascular disease (5, 6). Immunosuppressive treatment is also a precondition for a more severe course of the disease. However, the potential effect of its long-term use is a matter of debate (7, 8). Some argue that the transplant patients might be at a higher risk of severe infection resulting from their impaired immune system, while others speculate that immunosuppressive therapy might be protective as it could address the COVID-19 induced cytokine storm (9, 10, 11, 12, 13).

Large European data became available later, after the first wave. Recent data show that CKD patients are at a higher risk than those with other known risk factors, including chronic heart and lung disease. According to the European Renal Association COVID-19 registry, which included 4,298 kidney failure patients, 28-day mortality was 20 % in 3,285 patients receiving dialysis and 19.9 % in 1,013 recipients of a transplant (7). The ERACODA database (1,073 patients) reported a 28-day case fatality rate of 25 % in 768 dialysis patients and 21.3 % in 305 kidney transplant recipients during the first wave (5). Other reports based on regional or national registries have also suggested lower mortality in kidney transplant patients than in haemodialysis patients (14, 15).

COVID-19 reported case fatality rates vary greatly between the countries owing to differences in public health policy, case ascertainment, and testing capacity. During the pandemic, a substantial number of patients died while waitlisted, due to dramatic reductions in organ donation and transplantation, reaching as high as 80 % in some countries of the European Union (4, 16). The early days of the pandemic came with plenty of unknowns affecting the healthcare community's ability to prepare for and perform transplants. At the beginning, hospitals were limiting surgical procedures to emergencies only in the effort to free up staff for COVID-19 patients and to preserve scarce resources such as personal protective equipment. Testing capacity was also limited. Additionally, there was an effort to avoid the risk of further infections which could arise from admitting more patients into hospitals than necessary. Transplants from deceased donors were limited to urgent situations only; while living donation programs were suspended amid the lockdown and fear of infection. However, it was shown that during the outbreak, the risk of being infected by SARS-CoV-2 was more than 4 times lower for kidney transplant recipients than for the haemodialysis patients, mainly because transplant patients can be managed at home, while haemodialysis still mostly takes place in hospital settings (4, 17). In the center, the haemodialysis patients were at a higher risk for COVID-19 related mortality, independently from the known risk factors such as: obesity, ischemic heart disease and lung disease (2). Data from Spain and Italy have shown a 30 % mortality of dialysis patients (18, 19). Recently published French data showed that the 30-day Covid-19-related mortality was significantly higher in kidney transplant recipients (KTRs) compared to non-transplant patients (17.9 % *vs* 1.4 %, p = 0.038) (20).

*Short summary of the impact of the COVID-19 pandemic on donation and kidney transplant program in Slovakia*

The first patient to test positive for SARS-CoV-2 virus in Slovakia was reported on 6.3.2020. The last DBD (donation after brain death) donor and transplantation of two kidneys and one liver before the state of emergency was declared (15.3.2020) were performed on 11.3.2020. Twelve days later, measures were taken to limit the transplant program to urgent life-saving procedures (heart, liver), and kidney transplants from living and deceased donors were stopped. Due to the favorable development of the pandemic in Slovakia, kidney transplants from living and deceased donors were resumed since 14.4.2020, the transplant program was cleared for all the procedures, provided that donors were RT-PCR tested and strict epidemiological measures were observed. During the summer months, procurement and transplantation activity intensified to the average level of 2019, which was the most successful year in the number of organ transplants in the history of Slovakia. All of the postponed kidney transplants from living donors were performed. The second wave of the COVID-19 crisis began in September 2020. For the purposes of our analysis, the COVID-19 morbidity/mortality in the group of patients after kidney transplantation was divided to two phases: the first phase of the second wave (hereinafter "first period") from 1.9.2020 to 31.12.2020, and the second phase of the second wave, connected with spread of the alpha variant as confirmed by sequencing (hereinafter referred to as the "second period") from 1.1.2021 to 31.3.2021, when the data collection for this analysis was concluded. While all four Slovak kidney transplant centers (the University Hospital in Bratislava, Banská Bystrica, Martin and Košice) proceeded uniformly during the first wave of COVID-19, during the second wave, when the new precautionary measures were enacted in an effort to avoid stopping the transplant program, the individual transplant centers proceeded according to their individual possibilities, taking into account the regional epidemic situation.

We present our experience with the development and impact of COVID-19 pandemic on patients after kidney transplantation in Slovakia. We focused on morbidity and mortality during the two waves of the COVID-19 crisis and tried to identify the risk factors for developing a severe course of the disease in KTRs. We compared morbidity and mortality of KTRs with the haemodialysis population.

## Materials and methods

In the retrospective multicentric analysis, we included SARS-CoV-2 positively tested patients after kidney transplantation monitored in all four transplant centers in Slovakia – the University Hospital in Bratislava, Banska Bystrica, Martin, and Kosice. The

data were collected for the period from March 6, 2020 to March 31, 2021. Positivity was confirmed by real-time polymerase chain reaction (RT-PCR) test. We recorded the age, time (months) after transplantation, diabetes mellitus and arterial hypertension history, BMI (body mass index) and graft function at the time of the test positivity, and telephone consultation with the transplant center by the patient or the treating physician from the hospital, where the infected patient was admitted in relation to COVID-19 and its treatment. We evaluated the type and doses/levels of immunosuppression and treatment with angiotensin-converting enzyme inhibitors (ACE-I) at the time of the test positivity.

The group of the patients was divided into three subgroups according to the COVID-19 pandemic period:

Subgroup 1: the first wave of COVID-19 crisis (March 6, 2020 – August 31, 2020).

Subgroup 2: the first period of the second wave (September 1, 2020 – December 31, 2020).

Subgroup 3: the second period of the second wave – prevalence of the alpha variant of SARS-CoV-2 as confirmed by sample sequencing (January 1, 2021 – March 31, 2021).

Further division based on the clinical course of the disease was into asymptomatic or moderate course – patients were treated at home; and severe course requiring hospitalization.

For the purposes of the analysis, the doses were unified and mycophenolic acid (MPA) was recalculated to mycophenolate mofetil (MMF). Similar approach was used in recalculation of methylprednisolone to prednisolone.

To compare the mortality rate to that of the haemodialysis patients, we employed information from 34 dialysis clinics reporting data to Nephrocare European Clinical Database (EuClid5).

Immunosuppression:

Immunosuppressive treatment of the patients consisted of cyclosporine (n=33 patients, 10.8 %) or tacrolimus (n=261, 85.6 %); mycophenolate mofetil/mycophenolic acid (n=272, 89.2 %) and prednisone (n=266, 87.2 %). Cyclosporine was administered at a starting dose of 6–8 mg/kg per day (twice daily) for the first 24 hours after transplantation, with a later dosage adjustment to maintain the following blood concentration levels: 200–400 ng/ml in month 1, 200–300 ng/ml in months 2–3, 150–250 ng/ml in months 4–6, and 100–200 ng/ml in months 6–12. Tacrolimus was administered for the first 1–2 days after transplantation at a dose of 0.2 mg/kg per day, aiming to target whole blood concentration at 10 to 15 ng/ml in month 1, 7 to 10 ng/ml in months 2–3, 6 to 8 ng/ml in months 4–6, and 5 to 7 ng/ml in months 6–12. Mycophenolate mofetil/mycophenolic acid was given at an induction dose of 2000 mg/1440 mg per day and a maintenance dose of 1000–2000 mg/760–1440 mg per day, later reduced according to the immunology risk status of the patient. The initial dose of 500 mg of 6-methylprednisolone was administered intra-operatively intravenously (IV), then 250–500 mg IV 1 or 2 days post-transplant, followed by oral prednisolone acetate tapering to 20 mg during the first month after transplantation, then 10 mg during months 2–3, and later 5 to 2.5 mg per day.

Cyclosporine A, sirolimus and azathioprine were used in a small group of the patients with longer time since transplant.

*Statistical analysis*

We used a certified statistical program, MedCalc version 13.1.2. (VAT registration no. BE 0809 344 640, Member of International Association of Statistical Computing, Ostend, Belgium), to perform statistical analyses. Continuous data were compared using the Student's t-test or the Wilcoxon rank-sum test as appropriate. The $\chi^2$ test and Fisher's exact test were used for categorical variables. Univariate and multivariate logistic regressions were used to assess monitored parameters in order to predict the risk of severe course and death. Statistically significant parameters assessed in the univariate analysis were entered in the multivariate model. Statistically significant parameters were also further analysed by the means of probit regression. We considered the p value of $< 0.05$ to be statistically significant.

## Results

In the pandemic year 2020, the donation program in Slovakia dropped by 28.6 % ($p<0.0001$) compared to 2019, which was the most successful year for organ transplants in the history of Slovakia. The number of kidney transplantations decreased by 33.5 % ($p<0.0001$), kidney transplantations from living donors were at a comparable level ($p=0.0767$). Compared to 2018, kidney transplantations decreased by 10.3 % ($p= 0.0001$) during the COVID-19 crisis in Slovakia (Fig. 1).

A total of 305 patients (210 men, 68.8 %) with confirmed SARS-CoV-2 positivity between March 6, 2020 and March 31, 2021 were included in our analysis. Basic characteristics of the group are shown in the Table 1. The median age was 54 years (52.7 ±12), the median body mass index was 29 kg/m$^2$ (29.6±18.3), 291 recipients (95.4 %) suffered from hypertension and 109 (35.7 %) from diabetes mellitus. Patients, who were longer after the kidney transplantation became ill more frequently, with the median of 68 months (84.8±64.3). Excellent graft function (eGFR; CKD-EPI≥1.5 mL/s/1.73 m$^2$) at the time of the first positive test was found in 27 cases (8.9 %), 121 patients (39.7 %) were in the second stage of chronic kidney disease (eGFR; CKD-EPI 1.49–1.0 mL/s/1.73 m$^2$), 120 (39.3 %) in the third stage (eGFR; CKD-EPI

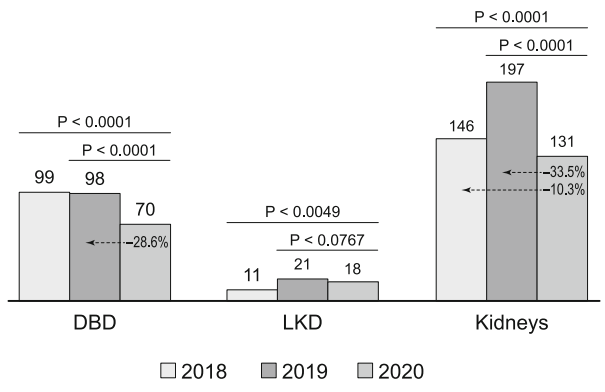


**Fig. 1. Kidney donation and transplant program in Slovakia – comparison of years 2018, 2019 and 2020.**

**Tab. 1. Demographic and clinical characteristics of patients (n = 305).**

| | |
|---|---|
| Age (years) | 52.7 ± 12 (median: 54) |
| Gender – men | 210 (68.8 %) |
| Time after transplantation (months) | 84.8 ± 64.3 (median: 68) |
| BMI (kg/m2) | 29.6 ± 18.3 (median: 29) |
| Diabetes mellitus | 109 (35.7 %) |
| Arterial hypertension | 291 (95.4 %) |
| ACE-I | 73 (23.9 %) |
| Tacrolimus | 261 (85.6 %) |
| Cyclosporin A | 33 (10.8 %) |
| mTOR-I | 15 (4.9 %) |
| MMF/MPA | 272 (89.2 %) |
| Azathioprine | 7 (2.3 %) |
| Steroids | 266 (87.2 %) |
| Average dose of MMF per day (mg) | 1255 ± 555 |
| Average dose of prednisolon per day (mg) | 6.3 ± 4 |
| eGFR (CKD-EPI) ≥ 1.5 mL/s | 27 (8.9 %) |
| eGFR (CKD-EPI) 1.49–1.0 mL/s | 121 (39.7 %) |
| eGFR (CKD-EPI) 0.99–0.5 mL/s | 120 (39.3 %) |
| eGFR (CKD-EPI) < 0.5 mL/s | 37 (12.1 %) |
| COVID-19 (03/2020–08/2020) | 3 (1 %) |
| COVID-19 (09/2020–12/2020) | 147 (48.2 %) |
| COVID-19 (01/2021–03/2021) | 155 (50.8 %) |
| Asymptomatic course of COVID-19 | 28 (9.2 %) |
| Moderate course of COVID-19 | 178 (58.4 %) |
| Serious course of COVID-19 | 99 (32.5 %) |
| Death from COVID-19 | 30 (9.8 %) |
| Consultation by patient | 192 (63 %) |
| Consultation by physician from hospital admitted the patent | 92 (92.9 %) |

ACE-I – angiotensin-converting enzyme inhibitor; BMI – body mass index; CKD-EPI – chronic kidney disease epidemiology collaboration; COVID-19 – coronavirus disease 2019; eGFR – estimated glomerular filtration rate; MMF – mycophenolate mofetil; MPA – mycophenolic acid; mTOR-I – inhibitor of mammalian target of rapamycine

**Tab. 2. Comparison of the group according to the course of disease (n = 277).**

| | Moderate course n=178 | Serious course n=99 | p |
|---|---|---|---|
| Age (years) | 51.4±12.3 | 55.5±10.8 | 0.0059 |
| Gender – men (%) | 64.5 | 72.4 | 0.1794 |
| Time after transplantation (months) | 80.9±59.9 | 85.5±68.1 | 0.5594 |
| BMI (kg/m2) | 30±23 | 30.4±8.5 | 0.8682 |
| Diabetes mellitus (%) | 28.4 | 48 | 0.0011 |
| Arterial hypertension (%) | 94 | 98 | 0.1280 |
| ACE-I (%) | 24.6 | 18.4 | 0.2359 |
| Tacrolimus (%) | 86.9 | 84.7 | 0.6117 |
| Cyclosporin A (%) | 8.7 | 12.2 | 0.3505 |
| mTOR-I (%) | 5.5 | 5.1 | 0.8874 |
| MMF/MPA (%) | 89.1 | 88.8 | 0.9391 |
| Azathioprine (%) | 2.7 | 1 | 0.3452 |
| Steroids (%) | 85.8 | 93.9 | 0.0419 |
| Average dose of MMF per day (mg) | 1251±557 | 1247±560 | 0.9544 |
| Average dose of prednisolon per day (mg) | 5.9±3.1 | 7.3±5.3 | 0.0056 |
| eGFR (CKD-EPI) ≥ 1.5 mL/s (%) | 9.3 | 6.1 | 0.3519 |
| eGFR (CKD-EPI) 1.49–1.0 mL/s (%) | 45.9 | 27.6 | 0.0028 |
| eGFR (CKD-EPI) 0.99–0.5 mL/s (%) | 35 | 44.9 | 0.1046 |
| eGFR (CKD-EPI) < 0.5 mL/s (%) | 9.8 | 21.4 | 0.0074 |
| Asymptomatic course of COVID-19 (%) | 1.7 | 0 | 0.1951 |
| Moderate course of COVID-19 (%) | 4.2 | 43.9 | 0.3973 |
| Serious course of COVID-19 (%) | 4.2 | 56.1 | 0.2709 |
| Death from COVID-19 (%) | 0.6 | 28.6 | <0.0001 |
| Consultation by patient (%) | 7.1 | 46.9 | <0.0001 |
| Consultation by physician from hospital admitted the patent (%) | 8.2 | 92.9 | <0.0001 |

ACE-I – angiotensin-converting enzyme inhibitor; BMI – body mass index; CKD-EPI – chronic kidney disease epidemiology collaboration; COVID-19 – coronavirus disease 2019; eGFR – estimated glomerular filtration rate; MMF – mycophenolate mofetil; MPA – mycophenolic acid; mTOR-I – inhibitor of mammalian target of rapamycine

0.99–0.5 mL/s/1.73 m$^2$), and 37 (12.1 %) with advanced graft dysfunction (eGFR; CKD-EPI < 0.5 mL/s/1.73 m$^2$).

In the first wave of COVID-19 crisis, only three positively tested patients (1 %) for SARS-CoV-2 were identified in Slovakia, the course of the disease was asymptomatic/moderate. During the second wave, the COVID-19 morbidity rose significantly, SARS-CoV-2 was identified in 302 KTRs (99 %), of which, in the first period of the second wave, it was 147 KTRs (48.2 %), followed by 155 (50.8 %) positively tested KTRs in the second period of the second pandemic wave (Tab. 1).

Criteria for the asymptomatic/moderate course of the disease were met by 206 patients (67.5 %), admission to the hospital was indicated in 99 KTRs (32.5 %) (Tab. 1). 192 positively tested patients (63 %) called the transplant centers and consulted the symptoms and the treatment (Tab. 1), more frequently during the second period of the second wave (54.9 % *vs* 71.6 %; p = 0.0028), more commonly with asymptomatic/moderate course of the disease (72.1 % *vs* 46.9 %); p < 0.0001) (Tab. 2). In 92 hospitalized patients (92.9 %), the physicians from the hospitals/COVID-19 departments to which the patients were admitted consulted the treatment with experienced nephrologists from the transplant centers, especially discontinuation of immunosuppressants, doses of steroids, and supportive antimicrobial treatment and a prevention of thrombosis (Tab. 2). There were no deaths recorded during the first wave, thirty patients (9.8 %) died during the second wave of COVID-19 pandemic, there was no significant difference between both periods of the second wave (Tab. 1). Elderly patients were hospitalized more frequently (p = 0.0059); for the whole set, in both univariate and multivariate analysis (Tab. 3), the age over 59 years was a risk factor for a more severe course and death. Another risk factor for hospitalization and death in the whole set, according to the univariate analysis, was diabetes mellitus, while in the multivariate analysis (Tab. 3), diabetes mellitus was only associated with a more severe course of the disease (OR [95 % CI]: 2.0433 [1.1812–3.5346]; p = 0.0106). The patients with advanced graft dysfunction defined by eGFR < 0.5 mL/s (Tab. 3), OR [95 % CI] had a worse prognosis associated with the risk of death: 4.8668 [1.7182–13.7849]; p = 0.0029). In contrast, better graft function was more common in the patients with a mild course (45.9 % *vs* 27.6 %, p = 0.0028).

We did not find any effect of arterial hypertension, BMI, time since transplantation, CNI, MMF/MPA, mTOR-I and ACE-I on the incidence and clinical course of COVID-19 in KTRs during the first and second waves of the pandemic (Tab. 2). At the time of finding of the infection, the patients with a more severe course and need for hospitalization (93.9 *vs* 85.8; p=0.0419) were more frequently treated with corticosteroids at a higher mean dose than the mild course group (7.3±5.3 *vs* 5.9±3.1; p=0.0056). While according to a univariate analysis, a lower dose of prednisolone (<10 mg) was a protective factor at the onset of the infection, the protective effect of low doses of corticosteroids was not confirmed by the multivariate analysis (Tab. 3).

We focused our interest in whether the spread of the alpha variant of the SARS-CoV-2 virus affected the course and risk factors of COVID-19 in kidney transplant patients. By comparing subgroup 2 (09/2020–12/2020) and subgroup 3 (01/2021–03/2021), we did not find any significant differences in the screened parameters depending on the period, when the patients became ill or tested positive for SARS-CoV-2 virus (Tabs 2, 4, 5).

Finally, we compared COVID-19 morbidity and mortality rates between KTRs and the patients on haemodialysis (HD). While among the patients after kidney transplantation, 14 % tested positive, in the haemodialysis cohort, there was up to 52 % positivity (p<0.0001). Mortality among the infected kidney recipients was 9.8 % *vs* 30 % (p<0.0001) in HD patients. Of the total set of KTRs in dispensary, a total of 1.4 % died in Slovakia during the COVID-19 pandemic by the end of March 2021, while in the population of HD patients it was up to 15.6 % (p<0.0001).

## Discussion

Our analysis confirmed that the risk group for a severe course of COVID-19 infection, as well as for death, are patients over 59 years, diabetes mellitus was found to be an independent risk factor for hospital admission. Our data correspond with the conclusions of the ERACODA register in which a 28-day mortality was primarily associated with elderly kidney transplant patients (5). The analysis by French authors comparing the course of COVID-19 infection in the patients after kidney transplantation with a non-transplant group also confirmed the significantly worse outcome of COVID-19 in the group of transplant patients over 60 years of age (19). Diabetes mellitus was confirmed as an independent risk factor for a serious course of COVID-19 in the group of patients after kidney transplantation (21). Advanced impairment of graft function at the time of infection was identified as another risk factor for poor outcome in the studied group of patients. The prevalence

**Tab. 3. Logistic regression – multivariant analysis of the whole group (n=305).**

| | Outcome hospitalization OR (95 % CI) | p | Outcome death OR (95 % CI) | p |
|---|---|---|---|---|
| Age at time of COVID-19 > 59 years | 1.0338 (1.0084–1.0598) | 0.0088 | 1.0548 (0.4111–2.7064) | 0.0003 |
| Diabetes mellitus | 2.0433 (1.1812–3.5346) | 0.0106 | 1.5203 (0.6722–3.4382) | 0.3144 |
| Steroids | 2.2203 (0.7417–6.6468) | 0.1539 | 2.7588 (0.5947–12.7976) | 0.1949 |
| Average dose of prednisolon < 10 mg/day | 1.0715 (0.9948–1.1540) | 0.0682 | 0.9968 (0.8952–1.1099) | 0.9527 |
| eGFR (CKD-EPI) 1.49–1.0 mL/s | 0.6306 (0.3499–1.1365) | 0.1250 | 1.0548 (0.4111–2.7064) | 0.9116 |
| eGFR (CKD-EPI) < 0.5 mL/s | 1.8697 (0.8584–4.0726) | 0.1151 | 4.8668 (1.7182–13.7849) | 0.0029 |

CKD-EPI – chronic kidney disease epidemiology collaboration; COVID-19 – coronavirus disease 2019; eGFR – estimated glomerular filtration rate

**Tab. 4. Logistic regression – multivariant analysis of the first period of the second wave 9/2020 – 12/2020 (n=305).**

| | Outcome hospitalization OR (95 % CI) | p | Outcome death OR (95 % CI) | p |
|---|---|---|---|---|
| Age at time of COVID-19 > 59 years | 1.0236 (0.9858–1.0629) | 0.2249 | 1.1274 (1.0291–1.2351) | 0.0100 |
| Diabetes mellitus | 1.6460 (0.7424–3.6495) | 0.2200 | 1.1388 (0.2634–4.9240) | 0.8619 |
| Steroids | 1.6702 (0.4093–6.8158) | 0.4747 | 0.5850 (0.1033–3.3146) | 0.5446 |
| eGFR (CKD-EPI) 1.49–1.0 mL/s | 0.5321 (0.2187–1.2943) | 0.1641 | 0.9893 (0.1544–6.3378) | 0.9910 |
| eGFR (CKD-EPI) < 0.5 mL/s | 2.2905 (0.7184–7.3025) | 0.1612 | 4.6798 (0.8971–24.4124) | 0.0671 |

CKD-EPI – chronic kidney disease epidemiology collaboration; COVID-19 – coronavirus disease 2019; eGFR – estimated glomerular filtration rate

**Tab. 5. Logistic regression – multivariant analysis of the second period of the second wave 1/2021 – 3/2021 (n=305).**

| | Outcome hospitalization OR (95 % CI) | p | Outcome death OR (95 % CI) | p |
|---|---|---|---|---|
| Age at time of COVID-19 > 59 years | 1.0277 (0.9940–1.0625) | 0.1079 | 1.0662 (1.0114–1.1240) | 0.0173 |
| Diabetes mellitus | 1.8921 (0.6464–5.5383) | 0.2445 | 1.9151 (0.6542–5.6069) | 0.2358 |
| Steroids | 5.7240 (1.2162–26.9392) | 0.0273 | 2.0176 (0.5970–4.9460) | 0.9973 |
| eGFR (CKD-EPI) 1.49–1.0 mL/s | 0.6117 (0.2729–1.3714) | 0.2328 | 1.0330 (0.3299–3.2345) | 0.9556 |
| eGFR (CKD-EPI) < 0.5 mL/s | 2.9415 (1.3321–6.4953) | 0.0076 | 4.4207 (1.0755–18.1711) | 0.0393 |

CKD-EPI – chronic kidney disease epidemiology collaboration; COVID-19 – coronavirus disease 2019; eGFR – estimated glomerular filtration rate

of the alpha variant in Slovakia did not affect the development of morbidity and mortality in the patients after kidney transplantation.

The pandemic heavily impacted both the dialysis care and organ procurement and transplantation activities: haemodialysis centers became a source of infections owing to the model of repetitive treatment in a closed community; peritoneal dialysis insertions, which could have protected CKD patients as they allow dialysis outside the hospital were postponed as non-urgent procedures (4, 15).

These factors also affected the situation in Slovakia. A quick understanding that restricting or stopping kidney transplants from deceased and living donors could lead to unnecessary deaths of the waitlisted patients led to setting the rules so that the procurement and transplantation program in Slovakia did not stop during the second wave of the COVID-19 crisis. Claims that transplant patients are at a high risk of infection, and it is better to keep them on the haemodialysis program have proved to be unsubstantiated. All the more so, given that the morbidity and mortality of the patients in hemodialysis centers in Slovakia was 52 % and 30 %, which was a higher rate compared to the ERA-EDTA Registry (7) and the ERACODA database (5) data, where 28-day mortality was 19.9 % and 25 %. The onset of morbidity and mortality in Slovakia during the second wave of the COVID-19 pandemic was also reflected in the increase in the number of infected KTRs, but compared to the haemodialysis population, the risk of infection and death was 3.7 times lower. According to the data of ERA-EDTA a EU National Competent Authorities on Organ donation and transplantation the risk of being infected by SARS-CoV-2 was more than 4 times lower for kidney transplant recipients than for hemodialysis patients, mainly because transplant patients can be managed at home, while haemodialysis still takes place mostly in hospital settings (4, 17). It should be noted that haemodialysis patients are generally older and have a higher prevalence of comorbid conditions than kidney transplant recipients (16). At the Slovak haemodialysis units, screening for COVID-19 was performed not only in symptomatic patients and as a post-contact screening, but also as a part of routine surveillance, whereas the transplant patients only underwent testing, when they presented with symptoms or after the contact with a positive person. On the other hand, lower morbidity and mortality among transplant patients may be explained by better habits to protect oneself from infection and by better opportunities to manage the treatment at home and remotely during the critical period of the pandemic (telemedicine, e-prescription), while haemodialysis still mostly takes place in hospital settings. Therefore, promoting transplantation is integral to fostering future preparedness for other mass infectious disease emergencies (4).

Unlike the first wave, the second wave in Slovakia was marked by a slow enacting of the precautions, greater benevolence, misinterpretation of negative test results (as being a "freedom pass") and also pandemic fatigue. Nevertheless, Slovakia was able to maintain the procurement and transplantation program. While donation and organ transplants in some European Union countries dropped by more than 80 % (7), in Slovakia it was only up to 33.5 %. Kidney transplants from living donors, with the exception of the first wave, continued without restriction and at the same level as in 2018 and 2019. No transmission of infection from the donor to the recipient or infection in the hospital during the short post-transplant period was observed. The first wave of the COVID-19 pandemic in Slovakia has shown that clear rules and strict anti-epidemic measures and their observance by kidney transplant patients as well as their family members are an efficient way to protect against the disease. An increased vigilance during a pandemic and the prevention of infectious diseases should be maintained not only shortly after transplantation, but also later, as patients being longer post-transplantation became infected more frequently (median: 5.7 years).

In January 2021, vaccination started in Slovakia for the health professionals and at-risk groups of the population, including patients with CKD, especially patients on dialysis and transplant patients.

The limitation of our analysis lies in the absence of data regarding the treatment of patients during hospitalization, since the patients were not hospitalised in a specialized COVID-19 center, consultation timing varied and thus, the treatment data would not be homogeneous. On the other hand, our analysis deals with the risk factors for a severe course of COVID-19 before the infection onset.

## Conclusion

The COVID-19 pandemic has had a substantial effect on morbidity and mortality in kidney replacement therapy patients affected by the disease, peaking in elderly and diabetic patients. Despite the higher risk of morbidity and mortality due to an impaired immunity, kidney transplantation from a deceased or living donor appears to be a safe treatment modality for patients with end-stage renal failure even during the COVID-19 pandemic. Mortality of the kidney transplant patients from COVID-19 is significantly lower than the risk of infection and death during haemodialysis treatment. It is of vital importance that in future pandemics, the nephrology community has a crisis management and protocols in place and be able to act swiftly to increase the safety of their patients and mitigate the damage to their health as much as possible. Transplant centers need to be flexible during the pandemic, adopting both short-term and long-term changes along the way. Important precautionary measures include an early vaccination of at-risk groups, including kidney transplant patients.

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