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Comparing the First and Second Wave of COVID-19 in Kidney Transplant Recipients: An East-European Perspective

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Keywords
COVID-19 · Epidemic wave · Kidney transplantation · Outcome

Abstract
Background: The present study examined whether patient characteristics, management, and outcome of kidney transplant recipients (KTx) with COVID-19 changed in the second versus the first pandemic wave. ***Methods:*** We reviewed all available data (demographics, medical history, comorbidities, therapeutic interventions, and outcome) on our KTx with COVID-19 during the first wave (March–September 2020, $n = 33$) and the second wave (October 2020–February 2021, $n = 149$) of the COVID-19 pandemic. ***Results:*** One hundred eighty-two out of our 1,503 KTx in active follow-up got COVID-19 during 12-month period, corresponding to a prevalence of 12.1%. No difference was found in age, gender distribution, comorbidities, body mass index, or baseline immunosuppression between the 2 COVID-19 waves. Bilateral COVID pneumonia was more frequent during the first wave. More KTx were managed as outpatients during the second wave (15 vs. 39%, $p < 0.01$). Calcineurin inhibitors were more sparingly reduced during the second wave, whereas antimetabolites were similarly reduced (91 vs. 86, p = ns). Admission to intensive care units was comparable between the first (27%) and second waves (23%). During the first wave, 8 out of 9 patients (89%) requiring intensive care died, whereas the mortality of the ICU patients in the second wave was 68% (23 deaths) ($p = 0.2$). The overall mortality was 24% during the first wave and 16% during the second wave ($p = 0.21$), while in-hospital mortality was identical between the COVID-19 waves (27%). Increasing age and poor allograft function were significant predictors of mortality. ***Conclusions:*** Most patient characteristics and outcome were comparable between the first 2 COVID-19 waves. More KTx were managed as outpatients without an overall negative impact on outcome.

Introduction

COVID-19 pandemic has claimed millions of lives and wreaked havoc on all aspects of human society. The early response in the spring of 2020 combined regional and national lockdowns, wearing face masks, curtailing indoor and outdoor activities, and imposing severe travel restric-

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tions [1, 2]. The massive economic and social costs and the ultimate decrease in new cases and fatalities in "the first wave" led to the lifting of some restrictions during the summer in Europe. Unfortunately, it became evident that COVID-19 both continued and gained pace in the Southern hemisphere and, eventually, a second wave of COVID-19 returned to Europe in the fall of 2020.

Romania, an East-European country of just above 19 million inhabitants, was among the countries which enforced a drastic, total lockdown lasting from late March to early June 2020. During the COVID-19 first wave, the peak incidence was reached on April 9th (441 confirmed new cases) and peak death toll of 35 cases on May 8, corresponding to a daily case fatality rate (calculated as the reported number of new COVID-19 deaths divided by the total number of active cases) of 0.4%. After a sustained and significant descent, followed by relaxing measures during summer, the infections started to rise again in mid-September 2020, reaching a second peak on November 18 with 10,269 confirmed new cases and 213 deaths on December 8, corresponding to a daily case fatality rate of 0.2%. No lockdown was enforced during the second COVID wave.

Organ transplant recipients were identified as a risk group due to a significant comorbidity burden and lifelong immunosuppressive medication, and several analyses have shown an increased risk for an unfavorable outcome following COVID-19 infection [3–5]. Given the need for a regular follow-up, transplanted patients usually maintain a close and frequent contact with their transplant center. Therefore, it is likely that COVID-19 cases in this patient group are promptly self-reported and more accurately identified, allowing for more correct insights into the frequency and outcome of the disease.

An increasing number of publications suggest that several differences may have existed in terms of epidemiology and outcome between the first and second COVID-19 waves [6–9]. The improved testing capacity and the increased knowledge about the pathology and treatment of COVID-19 but also the emergence of mutant virus strains may have been responsible for the different patterns increasingly reported in various settings. The limited data comparing the first and second waves of the COVID-19 in kidney transplant recipients (KTx) reveal diverging results between countries and have several significant limitations such as few patients or a selection bias toward hospitalized cases [10, 11]. We hereby present a comparison between the first and second waves of the COVID-19 pandemic at an East-European kidney transplant center, after the remission of the second wave.

Patients and Methods

Patient Selection

We performed a retrospective review of all patients who underwent kidney transplantation at the Clinical Institute of Urology and Renal Transplantation in Cluj-Napoca, Romania, who got sick with COVID-19 during the first and second waves of the COVID-19 pandemic. SARS-CoV-2 infection was defined as a positive result for SARS-CoV-2 RNA on real-time polymerase chain reaction assay of a nasopharyngeal swab. Both asymptomatic KTx and patients developing typical symptoms such as temperature >38°C, respiratory, gastrointestinal, neurological, or general symptoms were included.

For the purpose of this article, the first wave of the pandemic was defined as the interval between the first reported case in Romania (February 26, 2020) and the start of the second wave. The start of the second wave was defined by a sustained 25% increase in new weekly cases compared with the previous week (September 28, 2020). The second wave was considered to have lasted until the week with the lowest number of new cases reported since the start of the second wave (February 14, 2021).

Patient Management

The COVID-19 treatment protocol recommended in Romania in the early phase of the pandemic (March–July 2020) was based on hydroxychloroquine and antiretrovirals, as previously described [12]. Antiretrovirals (lopinavir/ritonavir, darunavir/ritonavir, or darunavir/cobicistat) were added in patients with mild and moderate forms and adequate renal function (GFR >30 mL/min/1.73 m^2). From mid-July 2020, dexamethasone and remdesivir (and favipiravir, from late 2020) were added to the treatment protocol in more severe cases, whereas hydroxychloroquine and retrovirals were no longer recommended. Antibiotics were also given at the discretion of the medical teams attending the patients. The use of anticoagulation using low molecular weight heparin was recommended in hospitalized patients from mid-April 2020 onward.

Immunosuppression was reduced by withdrawing the antimetabolite (mycophenolate mofetil or mycophenolic acid) with or without adjustment of calcineurin inhibitors. Tacrolimus was withdrawn in all patients receiving antiretrovirals and adjusted to maintain a trough level of 4–6 ng/mL in the other patients. Steroids were either kept at the maintenance dose or converted to IV for stress dosing.

All available medical records were reviewed and data on demographics, medical history, comorbidities, therapeutic interventions (antivirals, changes in immunosuppression, corticosteroid therapies, and respiratory support), and outcomes were collected and analyzed. Disease severity was classified from mild to critical [13]. The comorbidity assessment was performed using the age-adjusted Charlson comorbidity index as previously described [14]. Charlson comorbidity index includes 19 different medical conditions, and each comorbid disorder is ranged from 1 to 6 points to sum an index score. Additional points were added for age, and each decade over the age of 50 years received 1 point. Kidney graft function (estimated glomerular filtration rate) was assessed on data collected 12 months before COVID-19 using the CKD-EPI formula. The study was approved by the Institutional Review Board of the Clinical Institute of Urology and Renal Transplantation (1/2021).

Table 1. Patient baseline data, COVID-19 management, and outcome

	All patients (n = 182)	First wave (n = 33)	Second wave (n = 149)	p value
Males[a]	120 (65.9)	24 (72.7)	96 (64,4)	0.363
Age, years[b]	51 (43–57)	52 (46–58)	50 (43–56)	0.544
Months from transplant[b]	93.5 (38.5–139.3)	91 (34–150)	94 (45–136)	0.695
First year after transplant[a]	11 (6.0)	3 (9.1)	8 (5.4)	0.638
BMI, kg/m^{2}[b]	26.6 (18.7–40.6)	27 (20.7–35.3)	26.4 (18.7–40.6)	0.209
CCI median, range[b]	3 (2–4)	3 (2–4)	3 (2–4)	0.968
CCI 2	69 (37.9)	12 (36.3)	57 (38.2)	0.756
CCI 3 or 4	90 (49.4)	18 (54.5)	72 (48.3)	
CCI 5 and over	23 (12.6)	3 (9.0)	20 (13.4)	
Comorbidities				
Hypertension[b]	144 (79.1)	24 (72.7)	120 (80.5)	0.318
Diabetes[b]	48 (26.3)	8 (24.2)	40 (26.8)	0.759
Cardiovascular[b]	59 (32.4)	9 (27.2)	50 (33.5)	0.485
Malignancy[b]	8 (4.3)		8 (5.3)	n/a
Dementia [b]	1 (0.5)	1 (3.0)		n/a
Obesity[b]	35 (19.2)	7 (21.2)	28 (18.7)	0.750
Baseline eGFR, median/range	49 (32.8–70.3)	53 (40–72)	49 (31–68.5)	0.265
Baseline immunosuppression[a]				
Triple regimen	138 (75.8)	26 (78.7)	112 (75.1)	0.62
Tacrolimus	152 (83.5)	30 (90.9)	122 (81.8)	0.2
Cyclosporine A	3 (1.6)	1 (3.0)	2 (1.3)	0.37
Rapamycin	4 (2.1)		4 (2.6)	n/a
Antimetabolites	177 (97.2)	33 (100)	144 (96.6)	0.31
Low-dose steroids	165 (90.6)	28 (84.8)	137 (91.9)	0.21
Disease severity				
Mild	73 (40.1)	13 (39.3)	60 (40.2)	0.93
Moderate	35 (19.2)	6 (18.1)	29 (19.4)	0.87
Severe	33 (18.1)	7 (21.2)	26 (17.4)	0.61
Critical	41 (22.5)	7 (21.2)	34 (22.8)	0.84
Radiological findings				
Abnormal findings (all types)	119/133 (89.4)	25/28 (89.2)	94/105 (89.5)	0.963
COVID-19 pneumonia	86/133 (64.6)	22/28 (78.5)	64/105 (60.9)	0.08
Bilateral pneumonia	54/86 (62.7)	22/22 (100)	32/64 (50)	**<0.001**
Outpatient	63 (34.6)	5 (15.1)	58 (38.9)	**0.008**
COVID-19 management				
MMF reduction/withdrawal	158 (86.8)	30 (90.9)	128 (85.9)	0.44
CNI reduction/withdrawal	68 (37.3)	20 (60.6)	48 (32.2)	**0.001**
HCQ	27 (14.8)	13 (39.3)	14 (9.3)	**<0.001**
Tocilizumab	8 (4.3)	1 (3.0)	7 (4.6)	0.62
Dexamethasone	74 (40.6)	15 (45.4)	59 (39.5)	0.59
Antiretrovirals	18 (9.8)	8 (24.2)	10 (6.7)	**0.003**
Remdesivir/favipiravir	38 (20.8)	5 (15.1)	33 (22.1)	0.37
Oxygen therapy	75 (41.2)	14 (42.4)	61 (40.9)	0.91
LMWH and NOAC	118 (64.8)	26 (78.7)	92 (61.7)	0.06
CRRT	7 (3.8)		7 (4.6)	0.19
Intensive care admission	43 (23.6)	9 (27.2)	34 (22.8)	0.62
Outcome				
Discharged	88/119 (73.94)	20/28 (71.4)	68/91 (74.7)	0.67
Dead	31/182 (17.0)	8/33 (24.2)	23/149 (15.4)	0.22

Data are reported as number/total number of available observations and (percent), or median and interquartile range (Q1Q3) and were analyzed with n/a, not applicable; CCI, Charlson comorbidity index; CNI, calcineurin inhibitors; CRRT, continuous renal replacement therapy; HCQ, hydroxychloroquine; LMWH, low molecular weight heparin; MMF, mycophenolate mofetil; NOAC, nonvitamin K antagonist oral anticoagulants; eGFR, estimated glomerular filtration rate. [a] χ^2 test or Fisher's exact test. [b] Mann-Whitney test.

Statistical Analyses

Discrete data are described by their absolute frequency and percentage. Continuous data are expressed as median and interquartile range unless otherwise stated. Given the relatively small group size and data distribution, the Mann-Whitney test was used for analyzing the differences between the 2 waves. A χ^2 test or Fisher's exact test was employed for analyses of contingency tables.

Univariate logistic regression analysis was used to assess independent risk factors of COVID-19-related death in patients with a kidney allograft. In the multivariate analysis, the covariates with a p value <0.3 in the whole cohort were included and the models were constructed for the cohort as well as for individual waves. Differences in COVID-19 therapy were not considered as factors in the multivariate analysis since the treatment followed a similar, national protocol. A log-rank test was used to evaluate the risk of death in the KTx with COVID-19. Statistica v. 13.5 (StatSoft, Oklahoma, OK, USA) was used for all statistical analyses. A p value <5% was considered significant.

Results

Patients

At the start of the COVID-19 pandemic, there were 1,467 KTx recipients alive and in follow-up at the Institute for Urology and Renal Transplantation in Cluj-Napoca. An additional 36 patients were transplanted during the study period, resulting in 1,503 KTx recipients at potential risk. In total, 182 KTx got sick with COVID-19 during the study period, corresponding to a prevalence of 12.1%.

Overall, the median patient age was 51 years and males represented 65.9% of the entire cohort. Ten patients (5.4%) received their transplants in the 12 months before their COVID-19 infection. Thirty-three KTx got sick with COVID-19 before October 1, 2020 (the first wave), whereas 149 KTx got infected after this date (the second wave). The characteristics of all 182 SARS-CoV-2-positive KTx recipients are detailed in Table 1, both as a single patient cohort and separately as 2 subgroups, according to the onset of COVID-19.

There was no significant difference in age, gender distribution, comorbidities, body mass index, or in terms of immunosuppression between the patients of the first and second COVID waves. Disease severity (i.e., mild, moderate, severe, and critical) was similar between the 2 outbreaks. However, KTx in the first wave had a trend toward more frequently developing COVID-19 pneumonia and had significantly higher bilateral pulmonary involvement.

Management

Patient management differed in many respects between the 2 waves, reflecting changing health policies and guidelines, accumulating knowledge about COVID-19, and increasing experience. Significantly more patients were managed on outpatient basis during the second wave (15 vs. 39%, $p < 0.01$). Hydroxychloroquine and antiretrovirals were all but abandoned during the second wave. A trend toward a lesser use of anticoagulants was also observed during the second wave (Table 1).

Likewise, immunosuppression was managed differently during the second COVID wave. Whereas antimetabolites were reduced in a similar proportion (91 vs. 86, $p > 0.05$), calcineurin inhibitors were more sparingly reduced or withheld during the second wave. The proportion of patients with unchanged immunosuppression remained similar and low (9 vs. 7%, $p > 0.05$). Around 40% of the transplanted patients developing COVID-19 required oxygen therapy in different forms, whereas 1 quarter were admitted to intensive care units similarly between the first (27%) and second waves (23%).

Outcome

Overall mortality was 24% during the first wave and 16% during the second wave ($p = 0.21$). Mortality for hospitalized patients was identical during both COVID-19 waves (27%). During the first wave, 8 out of 9 patients (89%) requiring intensive care died, whereas the mortality of the ICU patients in the second wave was 68% (23 deaths) ($p = 0.2$).

In the univariate analysis, age, baseline eGFR, increasing comorbidities, and hypertension proved to be significant independent predictors for death for the whole cohort (Table 2). Baseline estimated glomerular filtration rate remained a significant prognostic factor in both waves, whereas age remained significant only in the second wave where the sample was larger (Table 3). No episode of acute rejection and no graft loss were recorded after at least 2 months of follow-up.

Discussion

Most of the published information on COVID-19 has been based on the data obtained over the first half year of the outbreak during "the first wave" of the pandemic, when the entire scientific and medical community rushed to understand and manage this complex and potentially lethal disease. Several risk factors such as male gender, advanced age, and some concurrent diseases and medications have been identified as risk factors for complicated disease or unfavorable outcomes [15–17]. However, the reappearance of a second outbreak of infections in the fall

Table 2. Unadjusted univariate logistic regression analysis for death as outcome after COVID-19 for the entire cohort of KTxs, and by waves

	All patients (n = 182)		First wave (n = 33)		Second wave (n = 149)	
	OR [95% CI]	p value	OR [95% CI]	p value	OR [95% CI]	p value
Age (years)	1.06 [1.02–1.11]	**0.006**	1.08 (0.98–1.18)	0.114	1.06 (1.01–1.11)	**0.030**
Male	0.93 [0.41–2.08]	0.855	0.53 (0.1–2.88)	0.459	1.04 (0.41–2.65)	0.932
BMI (kg/m^3)	1.02 [0.92–1.12]	0.716	1.01 (0.8–1.27)	0.933	1.1 (0.91–1.13)	0.798
Months after transplant	1.00 [0.997–1.01]	0.324	1 (0.99–1.01)	0.775	1 (1–1.01)	0.311
CCI						
2 (reference)		**0.031**		0.156		0.101
3 or 4	3.66 [1.30–10.32]	**0.014**	4.23 (0.43–41.87)	0.217	3.49 (1.09–11.17)	**0.036**
5+	4.52 [1.23–16.61]	**0.023**	22 (0.94–515.87)	0.055	3.31 (0.74–14.76)	0.116
eGFR at baseline	0.95 [0.93–0.97]	**<0.001**	0.94 (0.89–0.99)	**0.029**	0.95 (0.92–0.97)	**<0.001**
Obesity	1.01 [0.38–2.69]	0.985	0.45 (0.05–4.46)	0.497	1.24 (0.42–3.7)	0.694
Hypertension	4.54 [1.03–19.96]	**0.045**	807,737,446.81 (0–0)	0.999	2.86 (0.63–12.98)	0.172
Diabetes	1.18 [0.50–2.77]	0.712	5.25 (0.91–30.22)	0.063	0.72 (0.25–2.09)	0.549
Antiviral						
None (reference)		0.334		0.657		0.335
Antiretrovirals	2.37 [0.75–7.49]	0.142	1.33 (0.19–9.27)	0.771	3.07 (0.69–13.6)	0.140
Remdesivir/favipiravir	1.28 [0.49–3.33]	0.608	2.67 (0.33–21.73)	0.360	1.1 (0.37–3.28)	0.871
Immunomodulatory	0.97 [0.37–2.57]	0.948	0.36 (0.06–2.15)	0.263	1.26 (0.39–4.14)	0.700
Corticosteroids	1.28 [0.59–2.80]	0.529	0.42 (0.07–2.53)	0.346	1.77 (0.73–4.33)	0.209
Anticoagulants	1.95 [0.82–4.64]	0.132	0.95 (0.15–5.99)	0.954	2.19 (0.81–5.94)	0.122
ACE inhibitors/ARB	1.17 [0.44–3.08]	0.758	1.33 (0.13–14.01)	0.811	1.08 (0.37–3.15)	0.893

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CCI, Charlson comorbidity index; eGFR, estimated glomerular filtration rate; BMI, body mass index; KTx, kidney transplant recipient.

of 2020, greatly surpassing the first wave in terms of number of infections and hospitalizations, raises several new questions whether "the second wave" follows a different pattern in comparison with the initial, first outbreak. Preliminary reports from Italy suggest that the second COVID-19 wave is less severe and deadly than the first one (8) but also that the demographics of patients who died with COVID-19, their treatment, and disease trajectory have largely changed over time [18].

Several early reports signaled that transplant recipients with COVID-19 ran a very high risk of unfavorable outcome [3, 19–21]. Besides several controversial interventions (i.e., hydroxychloroquine and antiretrovirals), decreasing immunosuppression was advocated already in the early days of the COVID-19 outbreak [20, 22]. However, as evidence and guidelines were initially lacking, reducing immunosuppression varied significantly between centers (from modest reductions to complete interruption), whereas the low number of patients precluded any substantial conclusions on the efficacy of any particular approach. As the evidence and experience accumulated, several guidelines were ultimately issued and immunosuppression management during COVID-19 has become more rational and structured [23]. Our analysis confirms a trend toward a more restrictive and rational approach of immunosuppression reduction, particularly that of calcineurin inhibitors during the second COVID-19 wave, which did not negatively impact the outcomes. The feasibility of outpatient management of transplanted patients with COVID-19 has been shown during the first wave of the pandemic [24–26]. In the current patient group, increasingly managing the COVID-19 patients on an outpatient basis appeared as the single most significant change in patient management between the first and second COVID-19 waves. The proportion of patients managed entirely as outpatients was similar to that of a large Swedish cohort [27]. Although we could not retrieve reliable data on KTx initially managed as outpatients and later progressing and requiring hospitalization, published data suggest that about a third of the patients initially managed as outpatients ultimately require hospitalization [25, 27]. This underscores the importance of recognizing the risk factors for progression toward hospitalization and the essential role of accurate self-monitoring and telemedicine [28], as the trend to initially manage transplanted COVID-19 patients with mild symptoms at home is likely to continue.

Table 3. Multivariate logistic regression analysis for death after COVID-19 in the cohort of KTxs and by waves

	Coefficient	OR [95% CI]	*p* value	*p* value (Hosmer-Lemeshow test)
All				
Age, years	0.060	1.06 (1.01–1.11)	**0.013**	0.172
eGFR baseline	−0.050	0.95 (0.92–0.97)	**0.000**	
HT	0.930	2.53 (0.53–12.14)	0.247	
Constant			0.033	
First wave				
Age, years	0.050	1.05 (0.95–1.16)	0.358	0.594
eGFR baseline	−0.060	0.95 (0.89–1.01)	0.074	
Hypertension	n/r	n/r	n/r	
Constant			0.999	
Second wave				
Age, years	0.060	1.06 (1.01–1.12)	**0.031**	0.022
eGFR baseline	−0.060	0.94 (0.92–0.97)	**0.000**	
HT	0.360	1.44 (0.28–7.35)	0.664	
Constant			0.102	

eGFR, estimated glomerular filtration rate; HT, hypertension; KTx, kidney transplant recipient.

Romania has 3 active kidney transplant centers and just over 3,000 KTx alive and in follow-up. This analysis from the largest Romanian transplant center, responsible for about half of the KTx in the country, provides a dynamic insight into this distinct patient population and the disease spanning over the first 12 months of the COVID-19 pandemic. The results suggest that the severity of the disease remained essentially unchanged and the patient profile did not change significantly over the first year. Most of the patients appeared to develop milder forms of the disease, which could be handled in an outpatient setting while maintaining a close contact between patients, primary health-care providers, and transplant physicians.

Part of the current data suggests that more KTx in the second wave developed milder disease forms with less pulmonary involvement. Unfortunately, the mortality during the second wave remained very high. Although the difference in mortality between the 2 waves did not reach statistical significance, the absolute numbers are strikingly similar to those of a larger Spanish cohort reporting 27 and 15% mortality during the first and second COVID waves, respectively [11]. This is in contrast with a smaller Belgian study, which found a similar mortality during the first 2 COVID waves [10]. During the first wave, Spain had disproportionately high prevalence, death toll, and mortality [29], whereas Romania and other East-European countries enforced a very strict lockdown and witnessed a limited outbreak. While refinements in patient management may have contributed to decreased mortality in the second wave, underdiagnosing mild cases during the first wave may have biased the analyses and results due to the identification of predominantly more severe cases seeking hospitalization.

As in previous other studies and larger analyses [3, 27, 30, 31], age remained the most important risk factor for unfavorable outcome. Furthermore, in line with several recent reports [29, 32], we found that the poor graft function has a significant predictive value for KTx death following COVID-19.

Our study has several limitations, mostly due to the unequal and relatively small size of the patient groups during the first 2 pandemic waves. The low number of cases during the first wave interfered with several statistical analyses. For this reason, we chose to extend "the first wave" beyond mid-June 2020, when the actual first wave actually ended, until late September 2020, when the second wave started. Moreover, insufficient testing during the early wave and asymptomatic cases may have led to an unknown number of undiagnosed cases. Asymptomatic COVID-19 in transplanted patients may range from 1.4 to 18% [11, 27] and may have represented a source of error. However, the noteworthy difference in infection numbers between periods with and without lockdown is likely due not to underdiagnosed cases but to the drastic lockdown measures enforced in the spring of 2020. This further emphasizes the life-saving potential of social distancing and stay-at-home orders as ways to minimize the

patient risk of COVID-19 exposure. We did not include detailed laboratory data due to missing data, a large proportion of outpatients lacking sampling during COVID-19, or variable parameters and sampling frequency between different hospitals.

As with all the other COVID-19 studies, this report presents an evolutionary experience where cases were likely managed differently throughout the study. To the best of our knowledge, this is the third report worldwide and the first from Central and Eastern Europe to assess and compare the impact of first and second COVID-19 waves on transplant recipients. In line with others, the study reveals a progression toward a more rational and individualized patient management. Whereas the prevalence greatly increased, the mortality remained much higher than in nontransplanted patients.

Statement of Ethics

The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study protocol was reviewed and approved by the Ethical Review Committee of the Clinical Institute for Urology and Renal Transplantation, who waived the requirement for informed consent for the retrospective chart review (01/2021).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

F.L.E.: designed the study, collected and analyzed data, wrote the draft, and reviewed and approved the manuscript; S.D.B.: analyzed data, wrote the draft, and reviewed and approved the manuscript; A.M.: collected and analyzed data, and reviewed and approved the manuscript; A.D.E.: collected and analyzed data, and reviewed and approved the manuscript; C.C.: collected and analyzed data, and reviewed and approved the manuscript; M.L.: collected and analyzed data, and reviewed and approved the manuscript; M.O.: designed the study, collected and analyzed data, wrote the draft, and reviewed and approved the manuscript.

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