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CLINICAL STUDY

Age and sex disparity in infectious complications after kidney transplantation

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ABSTRACT

OBJECTIVES: The aim of our analysis was to find whether there are sex and age differences in the incidence of single and repeat infection after kidney transplantation (KT).

BACKGROUND: Potent immunosuppression lowers the incidence of acute graft rejection but increases the risk of post-transplant infections. Older adults and females are at high risk of infections leading to poor outcome after KT.

MATERIALS: Our analysis consisted of 66 males and 34 females after KT, average age 47.5±12.6 years.

RESULTS: Female gender was a RF for the incidence of infection in general (p=0.0054), recurrent (p=0.0239), bacterial (p=0.0125) and mycotic infection (p=0.0103), recurrent bacterial infection (p=0.0258) 1st month after KT, RF for the incidence of infection in general (p=0.0218), bacterial (p=0.0186), mycotic (p=0.0318), recurrent (p=0.0216), recurrent bacterial infection (p=0.0368) from 1st to 6th month after KT and RF for the incidence of bacterial (p=0.0144), single (p=0.0355), recurrent (p=0.0007) and single bacterial infection (p=0.0309) 6 months after KT. Age >60 years was not found as a RF for the incidence of single, repeat infection regarding its aetiology.

CONCLUSION: We found significant sex differences in the incidence of single and repeat infections in different time intervals after KT *(Tab. 4, Fig. 3, Ref. 31)*. Text in PDF *www.elis.sk*

KEY WORDS: kidney transplantation, gender disparity, sex disparity, infection, acute kidney rejection.

Abbreviations: ATG – anti-thymocyte globulin, CKD – chronic kidney disease, CKD-EPI – chronic kidney disease epidemiology collaboration, CMV – cytomegalovirus, CVC – central venous catheter, dnDSA – de novo donor specific antibody, eGFR – estimated glomerular filtration rate, ESKD – end-stage kidney disease, FSH – follicle-stimulating hormone, G-CSF – granulocytes colony stimulating factors, GnRH – gonadotropin-releasing hormone, ICU – intensive care unit, IRAK1 – interleukin 1 receptor-associated kinase, KT – kidney transplantation, LH – luteinizing hormone, MMF – mycophenolate mofetil, MPA – mycophenolic acid, PTDM – post-transplant diabetes mellitus, RF – risk factors, TLR7 – toll-like receptor 7, UC – urinary catheter, UTI – urinary tract infection

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Introduction

Kidney transplantation (KT) represents the most effective mean of renal replacement therapy with superior outcomes (survival rate, quality of life) compared to dialysis. The increase in prevalence of end-stage kidney disease (ESKD) is greater than the increase in its incidence, therefore the dialysed population is rapidly ageing (1, 2). Despite the mean age of kidney transplant recipients have been increasing, the survival advantage of the KT in the older recipients has not been clarified (3). Many age-related factors can jeopardize the outcome of KT such as: different pharmacokinetics of the immunosuppression (IS) and weaker immune system increasing their susceptibility to opportunistic infections (4, 5). The importance of an adequate IS for older patients was first outlined by Meier-Krieshe et al, who reported an increased susceptibility not only to infections, but also a vulnerability to rejections (6, 7). Generally, it is known that sex broadly influences the host immune response (8, 9). Traditional risk factors for urinary tract infection in KT recipients include females sex, age, delayed graft function, ureteral stent use (10). Several sources of evidence suggest that sex bias in infection is driven not only by anatomical differences, but also because of genetic and hormonal disparity.

Materials and methods

The study has a retrospective non-contemporaneous design and consisted of patients after KT in Transplant center Martin, Slovakia from 1st January 2015 to 31st December 2019. Induction IS protocol included anti-thymocyte globulin (ATG) given 3 days starting day 0 along with pulse methylprednisolone 500 mg on day 0 and 1 day after KT. Maintenance IS treatment consisted of either of mycophenolic acid (MPA) either as a mycophenolate sodium with starting per oral dose 720 mg twice a day (daily dose 1440 mg) or mycophenolate mofetil (MMF) 1 g twice a day. In order to maintain the consistency of the whole study group, we considered dose 1 g of MMF (as a MPA prodrug) equivalent to 720 mg mycophenolate sodium or MPA. Tacrolimus was administered orally with initial dose 0.2 mg/kg of patient's weight adjusted based on through levels to target 10–15 ng/ml 3 months after KT, 6–10 ng/ml 3 to 6 months after KT and thence 3–6 ng/ml. The initial dose of prednisolone was 20 mg daily with weaning on 15 mg/day 2 weeks after KT, 10 mg/day 1 month after KT, 7.5 mg/day 4 months after KT to minimal maintenance dose 5mg starting 1 year after KT. For infection prophylaxis, all the patients received sulphamethoxazole/trimethoprim (800/160 mg) daily for 6 months. Based on induction IS with ATG, all the patients received cytomegalovirus (CMV) prophylaxis starting with ganciclovir administered intravenously, dose adjusted on eGFR, switched to valganciclovir with standard daily dose 900 mg once a day (reduced with a decreased eGFR) for 3 months. For mycotic prevention, fluconazole in daily dose 100 mg a day for 3 months was given. Cefuroxime was given as a prophylaxis prior to surgical procedure 1500 mg i.v and then 750 mg every 8 hours for 24 hours. For mycotic infection prevention, 50 mg of fluconazole once a day was given perorally for 3 months.

The baseline information collected included the age at time of KT, weight and height of the recipient, gender, primary disease associated with ESKD, type and duration of dialysis treatment in months, duration on waiting list (days), type of kidney donor: standard donor criteria, living donor, extended criteria donor defined as a donor older than 60 years, or donor over age 50 with at least two of the following: history of arterial hypertension, serum creatinine level > 133 μmol/l or cause of death from cerebrovascular accident. In our analysis, we included actual and maximal panel – reactive antibodies, cold ischemia time, delayed graft function defined as a need for dialysis 7 days after KT.

We monitored the incidence of infectious complications in the period of 12 months after kidney transplantation. We divided the observed period into 3 intervals: within 1 month after the KT, from the 1st to the 6th month and from the 6th to the 12th

Tab. 1. The basic characteristics of the patients.

Basic parameters	
Males (%)	66
Age (years)	47.5±12.6
Cumulative dose of ATG (mg/kg)	3.6±0.7
Dialysis time (months)	33.4 (median 18.5)
Duration on WL (days)	412 (median 134)
ECD (%)	36
Compatibility index	16.2±6.1
PRA actual (%)	1.2 (median 0)
PRA maximal (%)	5.6 (median 1)
CIT (min)	738 (670)
DGF (%)	11
ACR (%)	13
AHR (%)	15
Graft function	
eGFR 1M (ml/min)	42.3±20
eGFR 6M (ml/min)	48.2±18.8
eGFR 12M (ml/min)	53.4±21
Serum creatinine level 1M (μmol/l)	187±113
Serum creatinine level 6M (μmol/l)	160±78
Serum creatinine level 12M (μmol/l)	150±80
Labs	
Leukopenia (%)	84
Leukocytes 1M (109/l)	3.9±1.4
Leukocytes 6M (109/l)	3.1±1.6
Leukocytes 12M (109/l)	5.1±1.6
Need for G-CSF (%)	13
Thrombocytopenia (%)	71
Platelets 1M (109/l)	120±47
Platelets 6M (109/l)	158±63
Platelets 12M (109/l)	171±55

ATG – antithymocytary globulin; WL – waiting list; ECD – extended criteria donor; PRA – panel reactive antibody; CIT – cold ischemia time; DGF – delayed graft function; ACR – acute cellular rejection; AHR – acute humoral rejection; eGFR – estimated glomerular filtration rate; G-CSF: granulocytes colony stimulating factor

Tab. 2. Aetiology, localization and severity of single, recurrent infection in observed intervals.

	Follow-up								
Etiology of infection	1 M			1 – 6 M			6 – 12 M		
	0	1	R	0	1	R	0	1	R
bacterial infection	54 %	21 %	25 %	27 %	18 %	55 %	43 %	14 %	43 %
viral infection	95 %	4 %	1 %	66 %	27 %	7 %	42 %	14 %	42 %
CMV infection	98 %	2 %	0 %	66 %	32 %	0 %	71 %	22 %	7 %
mycotic infection	92 %	6 %	2 %	86 %	11 %	3%	71 %	22 %	7 %
MDR	61 %	18 %	21 %	46 %	15 %	39 %	67 %	16 %	17%
Localization of infection	1 M			1 – 6 M			6 – 12 M		
	0	1	R	0	1	R	0	1	R
UTI	56 %	24 %	24 %	33 %	20 %	47 %	19 %	19 %	35 %
RTI	97 %	2 %	1 %	65 %	29 %	6 %	51 %	21 %	0 %
GI	96 %	4 %	0 %	91 %	6 %	3 %	83 %	4 %	3 %
bloodstream	100 %	0 %	0 %	93 %	5 %	2 %	90 %	4 %	0 %
other	91 %	6 %	3 %	78 %	16 %	6 %	66 %	9 %	2 %
Infection severity	1 M			1 – 6 M			6 – 12 M		
	0	1	R	0	1	R	0	1	R
hospitalization	96 %	3 %	1 %	81 %	11 %	8 %	69 %	21 %	10 %
ICU	100 %	0 %	0 %	94 %	4 %	2 %	91 %	7 %	2 %
vasopressors	100 %	0 %	0 %	99 %	1 %	0 %	98 %	2 %	0 %
Infection in general	1 M			1 – 6 M			6 – 12 M		
	0	1	R	0	1	R	0	1	R
	47 %	25 %	28 %	10 %	23 %	67 %	26 %	19 %	55 %

CMV – cytomegalovirus, MDR – multi-drug resistance, UTI – urinary tract infection, GI – gastrointestinal, RTI – respiratory tract infection, ICU – intensive care unit, 0 – no infection, 1 – single infection, R – recurrent infection, M – month

month after the KT. The patients underwent regular check-ups at the Transplant and Nephrology Outpatient Clinic at regular intervals – weekly up to 3 months after KT, every two weeks from 3rd to 6th month after KT, every month from 6th to 12th month after KT. We monitored the mean tacrolimus level (ng/ml) during the regular check-ups and the daily dose of MPA (mg) at 1, 6 and 12 months after KT, whether the patient was taking corticosteroids. During the observed period, we recorded the level of creatinine at the 1st, 6th and 12th month after KT (μmol/l) followed by the calculation of glomerular filtration according to CKD-EPI (ml/min/1.73 m^2).

During the observed period, we recorded the incidence of infection according to the aetiology to bacterial, viral, fungal, parasitic infections and CMV infection. Infection was defined on the basis of clinical and/or laboratory signs of infection. A separate group of infections was CMV infection verified by PCR. We considered copy number > 1000/ml to be a significant replication of CMV. In the case of detection of the etiological agent, we determined the sensitivity to individual antibiotics. Based on the results, we determined the incidence of multidrug-resistant strains. Multidrug resistance was defined as the resistance of to at least 1 antibiotic drug from at least 3 different groups of antibiotics. In our analysis, we recorded the incidence of infections by location for infections of the urogenital, respiratory, gastrointestinal system, bloodstream and others (skin infection, surgical wound). Urogenital tract infection was diagnosed based on clinical signs (dysuric disorders, fever, increased frequency of urination, palpable sensitivity in the suprapubic area) and/or isolation of the infectious agent from urine. Respiratory infection was defined on the basis of clinical signs (cough, dyspnea, fever) and/or imaging methods (X-ray/CT-verified bronchopneumonia) and/or culture of an infectious agent from sputum or bronchoalveolar lavage. Blood infection was defined on the basis of clinical signs of infection and the presence of an infectious agent in the blood culture, with a potential contamination ruled out by culture examination of the skin smear at the blood culture site. Another infection was defined based on the clinical signs of a local infection and/or the verified presence of an infectious agent from the wound. We recorded whether the patient had an infection during the study period requiring the hospitalization, intensive care, and the need for vasopressoric support. We monitored the occurrence of acute humoral and cellular rejection verified histologically by a needle graft biopsy or by the presence of de novo donor specific antibodies (dnDSA) detected by Luminex. We also recorded the incidence of leukopenia, defined as a decrease in white blood cells bellow $3.9x10^9$/l and the incidence of thrombocytopenia defined as a decrease in platelets below $140x10^9$/l, during the observed period we recorded the lowest value of leukocytes and platelets and the need for granulocytes colony stimulating factors (G-CSF) in the event of a decrease in absolute neutrophil count $<0.5x10^9$/l at a dose of 48 IU administered subcutaneously daily for 3 days.

We used a certified statistical program, namely MedCalc version 13.1.2 (MedCalc Software VAT registration number BE 0809 344,640, Member of International Association of Statistical Computing, Ostend, Belgium). Categorical variables were presented as the counts and weighted percentages. Comparisons of continuous variables between the groups were performed using parametric (*t*-test) or non-parametric (Mann-Whitney) tests; associations between the categorical variables were analysed using the $\chi 2$ test and Fisher's exact test, as appropriate. Logistic regression was used for multivariate analysis for the independent predictors of the infection's incidence. By probit dose regression, we correlated the effect of immunosuppression and the incidence of infections. The p value < 0.05 was considered to be statistically significant.

Ethical approval: All the procedures involving human participants have been approved according to the ethical standards of the institutional ethical committee (University hospital Martin), including the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent for the included participants was checked and approved by University hospital's ethical committee and all the signed informed consents have been archived for at least 20 years after research was completed. The clinical and research activities being reported are consistent with the principles of the Declaration of Istanbul, as outlined in the Declaration of Istanbul on organ trafficking and transplant tourism.

Results

During the study period, 100 kidney transplant recipients were included, 66 males (66 %) and 34 females (34 %). Basic characteristics of the participants, as well as immunosuppression level, graft functions and laboratory parameters are shown in the Table 1.

Based on age, we divided the patients to the group younger than 60 years and then group of the patients older than 60 years. We observed a positive culture finding of urinary catheter (UC) in 71 % of the patients younger than 60 years, compared with 81 % of the patients older than 60 years, a positive culture finding of central venous catheter (CVC) in 24 % of the patients younger, respectively in 25 % of the patients older than 60 years,

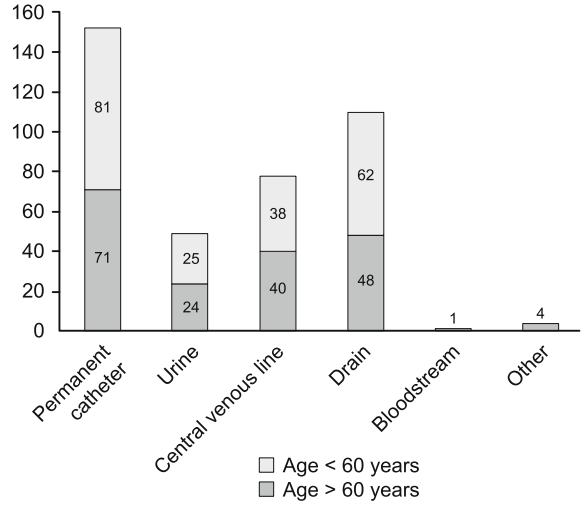

Fig. 1. Source of infection after kidney transplantation - age distribution (data are given in percentages).

Tab. 3. The independent risk factors for the incidence of infection.

	Odds ratio	95 % CI	p
The incidence of infection M1			
Gender (male)	0.2286	0.0808–0.6470	**0.0054**
Age > 60 years	1.4019	0.3845–5.1115	0.6088
The incidence of infection M6			
Gender (male)	0.0707	0.0073–0.6804	**0.0218**
Age > 60 years	1.1996	0.2380–6.0458	0.8255
The incidence of infection M12			
Gender (male)	0.4866	0.1648–1.4369	0.1923
Age > 60 years	1.0033	0.2571–3.9150	0.9962
The incidence of bacterial infection M1			
Gender (male)	0.2947	0.1130–0.7686	**0.0125**
Age > 60 years	1.5420	0.4387–5.4192	0.4995
The incidence of bacterial infection M6			
Gender (male)	0.0300	0.0016–0.5562	**0.0186**
Age > 60 years	1.1018	0.1420–8.5520	0.9261
The incidence of bacterial infection M12			
Gender (male)	0.3007	0.1148–0.7876	**0.0144**
Age > 60 years	1.4996	0.4141–5.4298	0.5371
The incidence of viral infection M1			
Gender (male)	0.0275	0.0359–2.1618	0.9853
Age > 60 years	1.9917	0.7748–2.4984	0.9993
The incidence of viral infection M6			
Gender (male)	0.9302	0.3614–2.3944	0.8808
Age > 60 years	0.6882	0.1839–2.5759	0.5789
The incidence of viral infection M12			
Gender (male)	0.5311	0.1753–1.6093	0.2632
Age > 60 years	2.4090	0.5454–106408	0.2460
The incidence of mycotic infection M1			
Gender (male)	0.0308	0.0022–0.4403	**0.0103**
Age > 60 years	0.9486	0.0462–19.4916	0.9727
The incidence of mycotic infection M6			
Gender (male)	0.2311	0.0607–0.8799	**0.0318**
Age > 60 years	3.9441	0.7648–20.3389	0.1011
The incidence of mycotic infection M12			
Gender (male)	0.5918	0.1344–2.6047	0.4878
Age > 60 years	2.5811	0.3128–21.2961	0.3785

positivity of the culture finding of abdominal drains in 48 % of the patients younger and 62 % of the patients older than 60 years. 24 % younger and 25 % older than 60 years had a positive urine culture finding. In the group of the patients younger than 60 years, 1 % of the patients had a positive haemoculture, 4 % of wound infections, neither of the two mentioned parameters occurred in the patients older than 60 years. We did not observe statistically significant differences between the incidence of culture findings between the age groups.

In terms of graft function, the mean eGFR in the group of the patients in the 1st month after transplantation was 42.3±20 ml/min, between 1 and 6 months after KT 48.2±18.8 ml/min, from 6th to 12th month, the eGFR was 53.4±21 ml/min. The creatinine value in the first month after KT was 187±113 µmol/l, between the 1st and 6th month 160±87 µmol/l and between the 6th and 12th month 150±80 µmol/l.

We monitored the incidence of single infection, recurrent infections, respectively an absence of the infection in the monitored periods: up to 1 month from KT, from 1 to 6 months and from 6 to 12 months after KT in terms of aetiology (bacterial, viral, fungal infections, CMV infection). In the monitored periods, we recorded the incidence of multidrug-resistant infections, the incidence of infections according to the affected organ

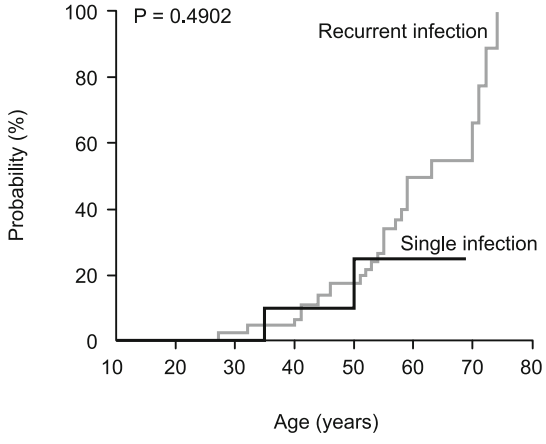

Fig. 2. Effect of tacrolimus levels on the incidence of infections 1st month after kidney transplantation.

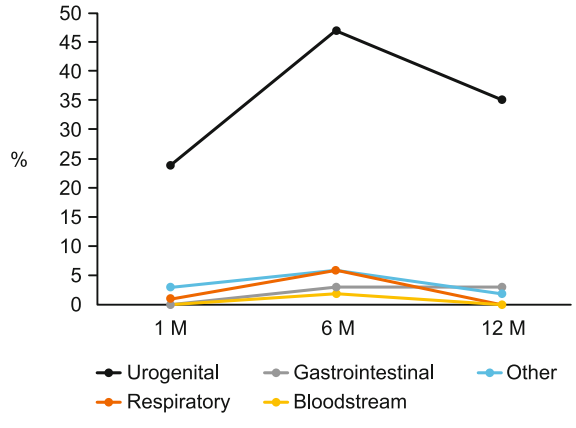

Fig. 3. Effect of MPA daily doses on the incidence of infections from 1st to 6th month after kidney transplantation.

system (urogenital, gastrointestinal, respiratory system infections, blood system infection – positive culture of blood cultures) and the severity of infection expressed by a need for hospitalization, intensive care unit (ICU) and vasopressoric support. Table 2 shows single, recurrent and no infection in observed intervals based on the aetiology, localization and severity of the infection.

Based on the age, we divided the patients into 2 groups: younger than 60 years and older than 60 years. We observed a positive culture finding of UC in 71 % of the patients younger than 60 years, compared with 81 % of the patients older than 60 years, a positive culture finding of CVC in 24 % of the patients younger, respectively in 25 % of the patients older than 60 years, positivity of the culture finding of abdominal drains in 48 % of the patients younger and 62 % of the patients older than 60 years. 24 % younger and 25 % older than 60 years had a positive urine culture finding. In the group of the patients younger than 60 years, 1 % of the patients had a positive hemoculture, 4 % of wound infections, neither of the two mentioned parameters occurred in the patients older than 60 years. We did not observe statistically significant differences between the incidence of culture findings between age groups (Fig. 1).

In our study, we confirmed female gender as a risk factor for the incidence of infection in general 1st month (p=0.0054) and from 1s to 6th month after KT (p=0.0218), for the incidence of bacterial infection 1st month (p=0.0125), from 1st to 6th month (p=0.0186) and from 6th to 12th month (p =0.0144). Female gender was also a risk factor for the incidence of mycotic infection 1st month (p=0.0103) and from 1st to 6th month (p=0.0318) after KT (Tab. 3).

By using a logistic regression, we identified the independent risk factors for the incidence of infections in the monitored periods. We included age >60 years and gender. In our study, we identified female gender as a risk factor for recurrent infection (p= 0.0239) and recurrent bacterial infection (p=0.0258) 1st month after KT. Female gender was also a risk factor for recurrent infection (p=0.0216) and recurrent bacterial infection (p=0.0368) 6 months after KT. Female gender was identified as a risk factor for singe infection in general (p=0.0355),

Tab. 4. Age and gender as the risk factor for single and recurrent infection after kidney transplantation.

	Odds ratio	95 % CI	p
The incidence of single infection M1			
Gender (male)	0.6396	0.2228–1.8364	0.4063
Age > 60 years	1.1773	0.2990–4.6361	0.8154
The incidence of single bacterial infection M1			
Gender (male)	0.6576	0.2120–2.0399	0.4680
Age > 60 years	1.7566	0.4357–7.0823	0.4284
The incidence of single viral infection M1			
Gender (male)	0.4379	0.0241–7.9636	0.5769
Age > 60 years	1.2406	0.8212–6.4399	0.9994
The incidence of single mycotic infection M1			
Gender (male)	4.1937	1.1105–8.0665	0.9983
Age > 60 years	3.2937	2.2905–5.0783	0.9992
The incidence of recurrent infection M1			
Gender (male)	0.2917	0.1001–0.8494	**0.0239**
Age > 60 years	1.5145	0.3656–6.2739	0.5671
The incidence of recurrent bacterial infection M1			
Gender (male)	0.2860	0.0952–0.8594	**0.0258**
Age > 60 years	1.0294	0.2176–4.8684	0.9709
	Odds ratio	95 % CI	p
The incidence of single infection M6			
Gender (male)	2.8054	0.7810–10.0778	0.1139
Age > 60 years	0.1496	0.0172–1.2994	0.0850
The incidence of recurrent infection M6			
Gender (male)	0.2496	0.0764–0.8155	**0.0216**
Age > 60 years	3.1537	0.7289–13.6443	0.1243
The incidence of single bacterial infection M6			
Gender (male)	0.6726	0.2090–2.1644	0.5060
Age > 60 years	0.4433	0.0780–2.5192	0.3587
The incidence of recurrent bacterial infection M6			
Gender (male)	0.3319	0.1179–0.9345	**0.0368**
Age > 60 years	1.8262	0.5182–6.4361	0.3487
The incidence of single viral infection M6			
Gender (male)	0.6621	0.2146–2.0423	0.4731
Age > 60 years	0.9369	0.2428–3.6154	0.9247
The incidence of recurrent viral infection M6			
Gender (male)	0.8678	0.0920–8.1854	0.9014
Age > 60 years	1.11577	0.1492–2.5796	0.9989
The incidence of single mycotic infection M6			
Gender (male)	0.3398	0.0743–1.5539	0.1640
Age > 60 years	2.2370	0.3902–12.8248	0.3662
	Odds ratio	95 % CI	p
The incidence of single infection M12			
Gender (male)	0.7478	0.1262–2.3351	**0.0355**
Age > 60 years	0.2296	0.0255–2.0700	0.1897
The incidence of recurrent infection M12			
Gender (male)	0.1330	0.0417–0.4246	**0.0007**
Age > 60 years	2.0030	0.4806–8.3481	0.3401
The incidence of single bacterial infection M12			
Gender (male)	0.2389	0.0651–0.8769	**0.0309**
Age > 60 years	1.3498	0.2738–6.6549	0.7125
The incidence of recurrent bacterial infection M12			
Gender (male)	0.5134	0.1936–1.3614	0.1803
Age > 60 years	1.0555	0.2889–3.8558	0.9348
The incidence of single viral infection M12			
Gender (male)	0.7828	02039–3.0046	0.7212
Age > 60 years	3.1236	0.6922–14.0966	0.1385
The incidence of recurrent viral infection M12			
Gender (male)	0.2485	0.0311–1.9826	0.1888
Age > 60 years	0.8304	0.0562–12.2653	0.8924
The incidence of single mycotic infection M12			
Gender (male)	0.6122	0.0995–3.7669	0.5966
Age > 60 years	1.4514	0.1966–10.7148	0.7150

single bacterial infection (p=0.0309) and recurrent infection (p =0.0007) 12 months after KT. Age more than 60 years was not defined as a risk factor for single or recurrent infection of any aetiology after KT (Tab. 4). Neither gender nor age more than 60 years were risk factors for the severity of infection defined by a need for hospitalization, ICU or vasopressors and also, they were not identified as risk factors for the acute graft rejection, however a delayed graft function was (p=0.0003). By Kepler-Meier curve, we did not find significant differences in the probability of the incidence of single, recurrent infection and age (Fig. 2).

Discussion

Generally, it is known that sex broadly influences the host immune response (8, 9). In healthy individuals, women exhibit an increased susceptibility and prevalence of urinary tract infection (11, 12). The prevalence of bacteriuria is approximately 10 % in adult women and 0.1 % in men, which is often attributed to anatomical differences between men and women, including urethra length (13). In our study, recurrent UTI were the most common type of recurrent infection based on aetiology thorough the 12-month follow-up. However, several lines of evidence suggest that sex bias in UTI is driven not only by dissimilar urethra length, but also by specific hormones, such as testosterone or estrogen over the course of lifetime – UTI incidence in male infants is nearly twice that of female infants. Indeed, the sex difference in UTI is the most pronounced in non-geriatric adults (11). The mean age of the patients in our study group was 47.5±12.6 years. Data suggests that the elimination of estrogen and experimental setting by ovariectomy leads to a higher bacterial burden following uropathogenic Escherichia coli infection compared with intact mice and also estrogen supplementation augments the expression of the antimicrobial gene human β-defensin 3 and strengthens urothelial junctions in vitro, which may positively impact barrier function in the bladder, protecting against infection (14). These findings suggest that estrogen may play a protective role against UTI and its loss may make women more vulnerable to infection. However, sex differences in the incidence of infections can be mediated by nonhormonal factors: the X chromosome expresses immune-related genes, such as: toll-like receptor 7 (TLR7) and interleukin-1 receptor-associated kinase (IRAK1) and also number of immune-associated microRNAs. While inactivation or silencing of one X chromosome in women would provide a dosage compensation of X-linked genes (15). The Y chromosome also influences immune gene expression, regulation, and susceptibility to both non-infectious autoimmune diseases and infection (16). The facts mentioned above could indicate, that women will be more resistant to infection, however in the patients with CKD there were hormonal changes negating the protective effect of hormones such as estrogen. The kidney is the key regulator of sex hormones in the patients with CKD (17). The onset of kidney disease results in ovarian dysfunction in women through disruption of the normal hypothalamus-pituitary-gonadal axis, directly related to the degree of CKD. Therefore, disturbances in the menstrual cycle and fertility become increasingly common as CKD progresses in women and amenorrhea and infertility are the norm when ESKD is reached (18). It is not clear, whether women with ESKD become menopausal at an earlier age due to comorbidities such as: diabetes mellitus, smoking, systemic lupus erythematosus (19, 20). Examining sex hormones is focused on the patients with ESKD, however information about fertility and related gynaecological issues are lacking in the earlier stages of CKD (21). As CKD progresses, tonic release of gonadotropin-releasing hormone (GnRH) regulating basal secretion of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) appears to remain normal, there is a loss of the physiological hypothalamic cyclic release of GnRH leading to loss of normal pulsatile pituitary gonadotropin secretion resulting in an impaired ovulation. Also hyperprolactinemia, caused by a decreased clearance of prolactin and it upregulated production due to CKD-mediated inhibition of dopaminergic activity (22). Hyperprolactinemia is believed to be a compensatory mechanism counteracting hypocalcemia as prolactin is one of the factors stimulating calcitriol synthesis (23). It can lead to a decreased cyclic GnRH activity and in the loss of pulsatile LH and FSH release, which leads to the decline and eventual absence of Estradiol release and lack of progestational changes in the endometrium (21). Some studies suggest, KT often, but not always restores menses and fertility (24). Menstrual disturbances were still common even after a successful KT (50 %) (25). It has been postulated, the hypothalamic-pituitary-gonadal axis is permanently altered following ESKD, although the normalization of hormonal status can be altered by immunosuppression (corticosteroids) and other medications (β-blockers) (26). The incidence of post-transplant diabetes mellitus (PTDM) is being reported more than 38.3 % in Slovakia (27). PTDM can cause menstrual disturbances through alterations of hypothalamus-pituitary-gonadal axis (28).

Kidney transplantation is the superior treatment of choice of ESKD including the older recipients for whom KT offers a survival benefit over dialysis and the outcomes such as mortality, graft loss are favourable (29. 30). Infections have been associated with a significant morbidity and mortality in older kidney transplant recipients, who are at a high risk of infections due to immunosenescence, frailty, functional impairment and multiple comorbidities (31). Moreover, in aged kidney transplant recipients, ESKD, stress of surgery and immunosuppressive therapies increase the risk of infections and poor outcome (4). According to literature, the incidence of UTI is increased in 1st year after KT due to the highest effect of immunosuppression and increased vulnerability of older kidney transplant recipients. As for another retrospective study, we found a different daily dose of mycophenolate mofetil and increased levels of tacrolimus as the risk factors for the incidence of infection (31). The study of Hemmersbach-Miller et al found an increased incidence of infections in kidney transplant recipients older than 65 years without an increased risk of acute graft rejection (10). In our study, the incidence of infections regarding its aetiology, severity was not significantly different in the patients older than 60 years. We did not perform analysis to compare the incidence of infections in the patients older than 65 years because of small number of the patients (8 %), but based on our results, the age 60 years is not a risk factor for an increased

incidence of infection, therefore there is no need to change the induction or maintenance immunosuppression as well as an antibiotic prophylactic therapy.

Conclusion

In our analysis, we found female sex as a risk factor for the incidence of several single and recurrent infections, we did not find the sex differences between the severity of the infections. It is undoubtedly clear we cannot change either induction or maintenance immunosuppression therapy based on the sex, however we can pay more attention if more risk factors, increasing the risk of infections, are present, such as PTDM, structural abnormalities of urinary tract, potent immunosuppressive antirejection treatment.

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