

Infectious Complications in Renal Transplant Recipients: Changing Epidemiology under Modern Immunosuppression

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Background: Immunosuppressive agents with higher potencies, such as tacrolimus and mycophenolate mofetil (MMF), have been introduced and widely accepted in clinical practice. This study evaluated the impact of these newer immunosuppressive drugs on the pattern and timing of post-kidney transplantation infections.

Methods: Data of kidney transplant recipients at the Seoul National University Hospital between January 1990 and November 2005 were analyzed. Recipients were divided into double immunosuppression (double group, n=198), triple immunosuppression including MMF (MMF group, n=253), and azathioprine (AZA, n=184) groups.

Results: The MMF group demonstrated higher graft survival and reduced rates of acute rejection within the fifth post-transplant year than both the AZA ($P<0.001$) and the double ($P<0.001$) groups. The overall incidence of infection in the first month was significantly higher in the MMF group (2.17/1,000 transplant-days) than in the AZA (0.73/1,000 transplant-days) and double (0.84/1,000 transplant-days) groups ($P=0.01$, ANOVA), and this was caused by viral infections that were significantly higher in the MMF (1.57/1,000 transplant-days) group than in the AZA (0.54/1,000 transplant-days) and double (0.67/1,000 transplant-days) groups. MMF was identified as a significant risk factor for viral infection ($P=0.013$; OR, 2.04; 95% CI, 1.16–3.60) in a multivariate logistic regression analysis.

Conclusions: The results suggest that viral infection rates were higher in the MMF group and should be considered the primary source of perioperative infectious complications in MMF-receiving recipients.

Key Words: Mycophenolate mofetil (MMF), Immunosuppressants, Infection, Virus, Graft survival, Graft rejection

중심 단어: Mycophenolate mofetil (MMF), 면역억제제, 감염, 바이러스, 이식편생존, 이식편거부반응

Introduction

Immunosuppression after solid organ transplantation has changed profoundly over the past decade. Tacrolimus (TAC) and mycophenolate mofetil (MMF) have rapidly gained acceptance among clinicians since their introduction in the mid-1990s and are widely used. The TAC and MMF combination is used as a replacement for cyclosporine A (CsA) and azathioprine (AZA) and is the most frequently prescribed immunosuppressive regimen in the United States(1,2). Clinical outcomes of renal transplantation have significantly improved in part due to the advances of immuno-

suppression(3). TAC-based immunosuppression has demonstrated significantly reduced rates of acute rejection and improved renal allograft function compared with CsA(4,5). Similarly, MMF treatment achieved a 50% reduction of histologically proven acute rejection episodes in renal allografts and functional improvement at 1 year post-transplantation(6,7), and a lower risk of graft loss at 5 years after transplantation compared with AZA(2).

The decline in the incidence of post-transplant infections and in infection-related morbidity and mortality has also contributed to the improvement of clinical outcomes. Infection-related mortality rates during the first post-transplantation year have demonstrated a significant decline in the past several decades: the current rate is less than 5%(8). However, infectious complications are still an impediment to successful clinical outcomes following transplantation(8).

Infections after solid organ transplantation tend to occur in generally predictable pattern that are largely

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dependent on both the recipient risk of infection and the intensity of immunosuppression(9). The introduction of immunosuppressive agents of higher potency, including MMF, may have resulted in modification of timeline for the development of common post-transplant infections (PTIs). However, there is limited information describing the impact of newer immunosuppressive agents on the pattern and timing of infectious complications following kidney transplantation(10). In addition, the changes in the real incidence of PTIs adjusted by the time at risk and the etiology have not undergone significant evaluation. We therefore assessed the impact of newer types of immunosuppressive drugs on the alteration of perioperative, early and late PTIs. We also analyzed the risk factors for development of PTIs.

Materials and Methods

1) Study population

Single kidney transplants performed at Seoul National University Hospital (SNUH) between January 1990 and November 2005 (n=734) were included in the study. Recipients' data were extracted from SNUH transplant database which contain their baseline clinical data and follow-up (weekly for months 1, monthly for months 2~6, every 6 months thereafter until 5 years after transplantation) biochemical data. The SNUH transplant database also included rejection episodes, including histopathologic findings and anti-rejection treatment, and descriptions of infectious episodes (clinical presentation, diagnostic work up, treatment, and outcome).

Recipients older than 18 years at the time of transplantation were included in the present study, and data for all recipients (n=635) were taken from SNUH transplant database. This study was approved by the Institutional Review Board of Seoul National University Hospital.

2) Immunosuppression and supportive care

Recipients who had undergone renal transplant procedures between 1990 and 1994 received double immunosuppressive therapy (CsA and corticosteroids); re-

cipients between 1995 and 2005 received a calcineurin inhibitor (CsA or TAC), an anti-metabolite (AZA or MMF), and corticosteroids. The dose of immunosuppressive drugs were: 1) cyclosporine (targeting a trough level of 100~250 ng/mL for the first 6 months and 40~80 ng/mL thereafter) or TAC (targeting a trough level of 8~12 ng/mL for the first months and 6~8 ng/mL for the months 2~5, and 4~6 ng/mL thereafter) 2) AZA (1~2 mg/kg per day) or MMF (1,000~1,500 mg per day) and 3) prednisolone (initially 1 mg/kg daily with rapid tapering to <5 mg per day). In some patients, 20 mg of basiliximab at day 0 and day 4 was used as an induction treatment. Protocol biopsies were not performed. Recipients with $\geq 25\%$ elevation in serum creatinine levels underwent ultrasound-guided percutaneous allograft biopsies. Episodes of biopsy-proven acute rejection (AR) were treated with intravenous methylprednisolone (500 mg per day for 3 days). With the first dose given 1 hour prior to the skin incision, intravenous cefazolin was given 48 hour perioperatively. Patients did not receive prophylactic agents for *Pneumocystis jirovecii* and cytomegalovirus (CMV). The Foley catheter was removed on the 4th postoperative day.

3) Definition and surveillance of infections

During the hospital stay, physical examination and laboratory investigations (including complete blood count with differentials, urinalysis, serum urea, creatinine and electrolytes) were performed daily. After discharge from hospital, patients were followed regularly in an outpatient setting. During these visits, detailed physical examination and laboratory investigation were performed to detect any infectious episodes. Patients with findings suggestive of infections (such as fever, diarrhea, leukocytosis, respiratory symptoms, and urinary symptoms) were undergone specific investigation, including anti-CMV antibody (Ig M and IgG), anti-Epstein Barr virus (anti-EBV) antibody (IgM and IgG), blood CMV p65 antigen testing, CMV DNA, chest X-ray, smear and cultures of blood, urine and sputum. For the present study, infectious episode definitions were adapted from a previous report(11) which is internationally accepted definition of infection in solid

organ transplant recipients: each infection was stratified into bacterial, viral, fungal, or mycobacterial categories according to clinical features and, if isolated, to original microorganisms. The analyzed time periods included the perioperative period (0 to 30 days after transplantation), the early post-transplant period (30 to 180 days after transplantation), and the late post-transplant period (beyond 180 days to 5 years after transplantation) (9).

4) Incidence of infection

Infection rates after kidney transplantation have been reported as the percentages of patients with infection, which were not adjusted by time at risk(12). It has therefore been difficult to evaluate the true incidence of infection in kidney transplant recipients. We calculated the incidence per 1,000 transplant-days using the number of days at risk as the denominator in the present study. The number of transplantation days was calculated as the sum of all days at risk of each kidney transplant recipient, as previously described(13). Days were stratified into above-mentioned periods, calculated from 1) transplantation day 0 to day 30 or the end of follow-up (death or graft failure) in the perioperative period, 2) day 30 to 180 or the end of follow-up (death or graft failure) in the early post-transplant period, and 3) day 181 to year 5 or the end of follow-up (death or graft failure) in the late post-transplant period.

5) Data analysis

Statistical analyses were performed using the SPSS software version 15.0, (SPSS Inc., Chicago, IL, USA). Data were expressed as mean \pm standard deviation (SD) values or as frequencies (percentages). Mean values were compared using the Student's t-test or paired t-test for continuous variables. Non-continuous variables were compared using the Pearson's chi-square test and the Fisher's exact test. Multiple logistic regression analysis was used to examine the influence of risk factors in the development of infection. Continuous variables were coded as dichotomous variables in this model. Variables significant at the $P < 0.10$ univariate level were included in the multivariate model using

forward stepwise logistic regression. Graft survival rates were determined by Kaplan-Meier analysis and the log-rank method. Univariate and multivariate analyses were conducted using Cox regression analysis. The confounders for both logistic and Cox regression analyses included age at transplantation, gender, number of human leukocyte antigen mismatches, number of transplantation procedures (first or re-transplant), diabetes mellitus, duration of pre-transplant dialysis, anti-metabolites (AZA or MMF), calcineurin inhibitor (TAC or CyA), monoclonal interleukin-2 receptor (IL-2R) antibody (basiliximab), AR episodes, CMV status, and herpes simplex virus (HSV) status. The transplant era divided as 1990~1994, 1995~1999, and 2000~2005 was included in multivariate analysis as a covariate. All tests were two-tailed, and statistical significance was established at P values of < 0.05 .

Results

1) Patient characteristics

Patients were categorized by immunosuppression type and intensity. Transplant recipients were treated with double (CsA and corticosteroids, $n=198$) or triple (CsA/TAC, AZA/MMF, and corticosteroids, $n=437$) immunosuppressive drugs. Patients treated with triple immunosuppressive drugs were subdivided into the AZA group ($n=184$) or the MMF group ($n=253$). All patients included in the study received corticosteroids as part of the immunosuppressive regimen, and 13.8% of patients were treated with monoclonal IL-2R antibody (basiliximab) as an induction treatment. Lastly, only 1.9% of recipients had a serologically mismatched CMV status (donor seropositive, recipient seronegative). Demographic and baseline characteristics are summarized in Table 1.

2) Graft outcome

The rate of AR within the 5th post-transplant year in the MMF group (14.6%) was significantly lower than rates in the AZA cohort (32.1%) and the double cohort (28.4%) ($P < 0.001$). MMF-treated recipients demonstrated a significant superiority in graft survival to AZA-treated recipients ($P=0.027$) or those not treated with anti-me-

Table 1. Demographic and baseline characteristics

	Double (n= 98)	AZA group (n=184)	MMF group (n=253)	P-value
Male (%)	130 (65.7)	131 (71.2)	153 (60.5)	0.02
Recipient age (years)	27.8 ± 12.5	28.8 ± 16.3	37.4 ± 14.7	<0.001
Body Mass Index (Kg/m ²)	21.2 ± 2.5	21.2 ± 2.8	21.9 ± 3.5	0.09
Donor age (years)	38.8 ± 12.5	36.1 ± 14.7	36.5 ± 11.5	0.80
Waiting time (months)	10.8 ± 14.9	16.3 ± 21.3	19.3 ± 31.1	0.30
Transplant duration (months)	117.4 ± 63.6	101.7 ± 40.6	52.4 ± 24.1	<0.001
2nd transplantation (%)	2 (1.0)	6 (3.3)	8 (3.2)	0.95
Number of HLA mismatches	2.02 ± 1.2	2.70 ± 1.3	2.75 ± 1.6	<0.001
Cause of ESRD (%)				<0.001
Diabetes mellitus	6 (3.0)	5 (2.7)	22 (8.7)	
Hypertension	9 (4.6)	8 (4.4)	34 (13.4)	
Glomerulonephritis	39 (19.7)	34 (18.5)	44 (17.4)	
IgA nephropathy	23 (11.6)	21 (11.4)	43 (17.0)	
ADPKD	3 (1.5)	12 (6.5)	10 (4.0)	
Deceased donor (%)	13 (6.6)	51 (27.7)	38 (15.0)	<0.001
AR episode (+) (%)	50 (28.4)	59 (32.1)	37 (14.6)	<0.001
Immunosuppressants				<0.001
Basiliximab (%)	2 (1.0)	3 (1.6)	91 (36.0)	
Calcineurin inhibitor (%)				
CsA (%)	198 (100.0)	181 (98.4)	110 (43.5)	
TAC (%)	0 (0.0)	3 (1.6)	143 (56.5)	
CMV D ⁺ /R ⁻ (%)	0 (0.0)	2 (1.1)	11 (4.4)	<0.001

Abbreviations: AZA, azathioprine; MMF, mycophenolate mofetil; HLA, human leukocyte antigen; ESRD, end stage renal disease; ADPKD, autosomal dominant polycystic kidney disease; AR, acute rejection; CsA, Cyclosporine A; TAC, Tacrolimus; CMV D⁺/R⁻, cytomegalovirus donor seropositive/recipient seronegative.

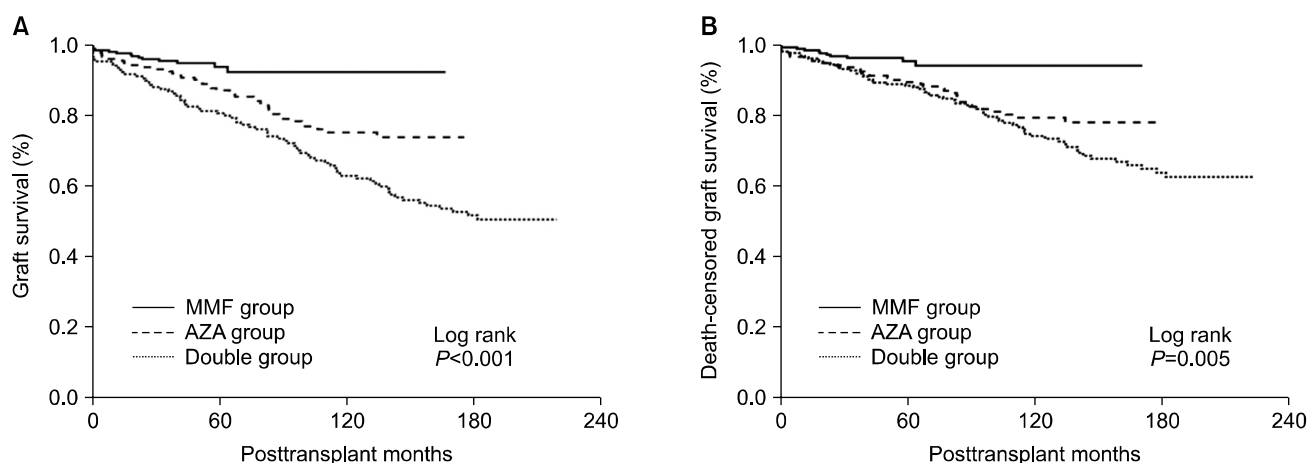


Fig. 1. Kaplan-Meier estimates of graft survival (A) and death-censored graft survival (B) up to year 15 after kidney transplantation according to the type of immunosuppression. A significant beneficial effect of MMF on graft survival and death-censored graft survival was identified.

Abbreviations: MMF, mycophenolate mofetil; AZA, azathioprine.

tabolites ($P<0.001$), as seen in Fig. 1A. MMF-treated patients also showed significant improvements in death-censored graft survival compared to AZA-treated patients ($P=0.019$) or patients not treated with anti-metabolites ($P=0.003$), as seen in Fig. 1B. Infection-related mortality rates were not significantly different among the double (2.0%), AZA (1.2%), and MMF (1.2%) groups ($P=0.76$). Human leukocyte antigen (HLA) mismatches >3 (hazard ratio (HR), 1.2; 95% confidence interval (CI), 1.02~1.41; $P=0.026$), double immunosuppression (HR, 3.63; 95% CI, 1.87~7.03; $P<0.001$), and infectious events (HR, 1.65; 95% CI, 1.04~2.60; $P=0.032$) were independent risk factors for graft loss by Cox Regression analysis. New-onset diabetes after transplantation (NODAT) (HR, 1.96; 95% CI, 0.95~4.05; $P=0.07$) and triple immunosuppression with AZA (HR, 1.91; 95% CI, 0.96~3.83; $P=0.07$) were associated with graft loss in the multivariate analysis. The transplant era (1990~1994, 1995~1999, and 2000~2005) did not induce significant impacts on graft survival.

3) Incidence of infections per time-period

A total of 212/635 ($n=35$ in the perioperative period, 47 in the early post-transplant period and 130 in the late post-transplant period) kidney transplant recipients

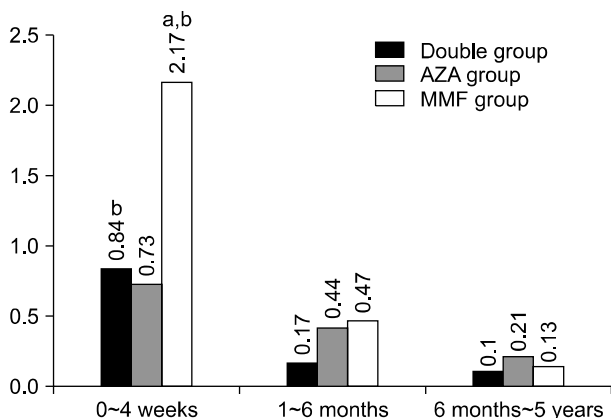


Fig. 2. True incidence rates of overall infections stratified by time periods. Incidence rates were calculated as infection episodes per 1,000 transplantation-days using the number of days at risk as the denominator. The MMF group demonstrated a significantly higher incidence of overall infections in the perioperative period compared to the double or AZA groups. ^a $P<0.05$, compared to other groups during the same period. ^b $P<0.05$, compared to other periods in the same transplant group. See Fig. 1.

suffered from more than one infectious episode within 5 years post-transplantation.

As shown in Fig. 2, the overall incidence of infection was significantly higher in the perioperative period compared to the late period in the double (0.84, 0.17 and 0.1 episodes per 1,000 transplant-days, respectively, for the perioperative, early, and late periods; $P=0.04$) and MMF groups (2.17, 0.47 and 0.13 episodes per 1,000 transplant-days, respectively, for the perioperative, early, and the late periods; $P<0.001$); this was not evident in the AZA group ($P=0.26$). The overall incidence of infection in the perioperative period was significantly higher in the MMF group (2.17/1,000 transplant-days) than in the AZA (0.73/1,000 transplant-days) and the double (0.84/1,000 transplant-days) groups ($P=0.01$). There was no difference in the overall incidence rates of early and late period infection among the three groups. The higher incidence of perioperative infection in the MMF group was largely attributed to increased rates of viral infection (Fig. 3). The MMF group had a higher incidence of viral infection (1.57 per 1,000 transplant-days) in the perioperative period than the double (0.67/1,000 transplant-days) and AZA (0.54/1,000 transplant-days) groups ($P=0.021$). Viral infections in the MMF group were associated with herpes zoster virus (HZV, $n=4$) and CMV ($n=2$) in this period. MMF recipients had a numerically higher incidence of perioperative bacterial infection compared to the double and AZA recipients but the difference did not achieve statistical significance (0.58, 0.17 and 0.18 per 1,000 transplant-days, respectively, $P=0.36$). There were no differences in the incidences of fungal or mycobacterial infections among the groups.

4) Factors predisposing post-transplant infections

Global risk factors related to infectious complications after kidney transplantation were compiled in a multivariate analysis (Fig. 4A), and included MMF use (odds ratios (OR), 2.38; 95% CI, 1.36~4.16; $P=0.02$), NODAT (OR, 2.35; 95% CI, 1.26~4.37; $P=0.01$), and AR episodes (+) (OR, 1.62; 95% CI, 1.15~2.28, $P=0.01$). Although AZA use, male gender, induction of antibody therapy, graft loss, and CMV D⁺/R⁻ appeared to be risk factors for infection by univariate analysis,

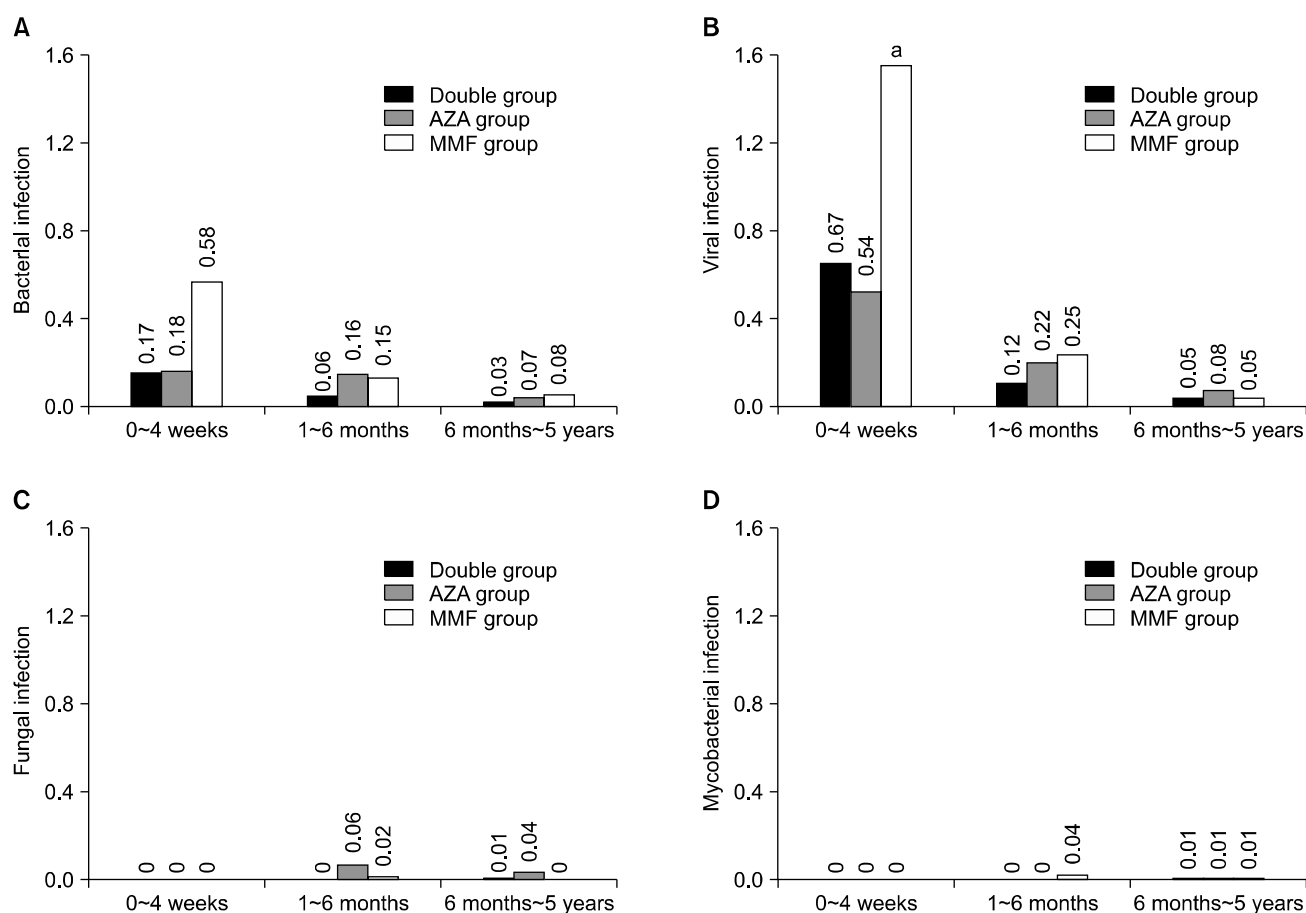


Fig. 3. True incidence rates of different categories of infectious complications: (A) bacterial, (B) viral, (C) fungal, and (D) mycobacterial infections. Higher incidence of perioperative infection in the MMF group was largely attributed to an increased rate of viral infection. ^a $P < 0.05$, compared to other groups during the same period. See Fig. 1.

sis, but were not identified to be significant in the final multivariate model. A more detailed analysis of risk factors for each category of infection was performed (Fig. 4B, C). MMF use (OR, 2.62; 95% CI, 1.38 ~ 4.98; $P < 0.01$) and male (OR, 1.85; 95% CI, 1.18 ~ 2.91; $P = 0.01$) were identified as risk factors for bacterial infections in perioperative period. Basiliximab use was associated with bacterial infection ($P = 0.09$). For viral infections, NODAT (OR, 2.30; 95% CI, 1.13 ~ 4.69; $P = 0.02$), MMF use (OR, 2.04; 95% CI, 1.16 ~ 3.60; $P = 0.01$), AR episodes (+) (OR, 1.57; 95% CI, 1.07 ~ 2.31; $P = 0.02$) were significant risk factors in perioperative period. CMV D⁺/R⁻ ($P = 0.11$) and HSV D⁺/R⁻ ($P = 0.06$) status exhibited trends towards risk of viral infection but was not significant in the multivariate analysis. The limited number of mycobacterial and fungal infections precluded risk factor analysis.

Discussion

Kidney transplantation is considered the treatment of choice for patients with end-stage renal disease; 97.5% of 1-year graft survival and 98.3% of death-censored graft survival rates were identified in recipients with triple immunosuppression including MMF (Fig. 1). Despite this success, transplants are continuously vulnerable to several infectious complications. The risk of infection is usually determined by the net state of immunosuppression, environmental exposures, and other comorbidities that contribute to recipient susceptibility to infection(14). Recent increases in the use of potent immunosuppressive agents have profoundly reduced the rate of rejection of transplanted organs while increasing patient susceptibility to infections(15). Therefore, the greatest challenge for clinicians is the main-

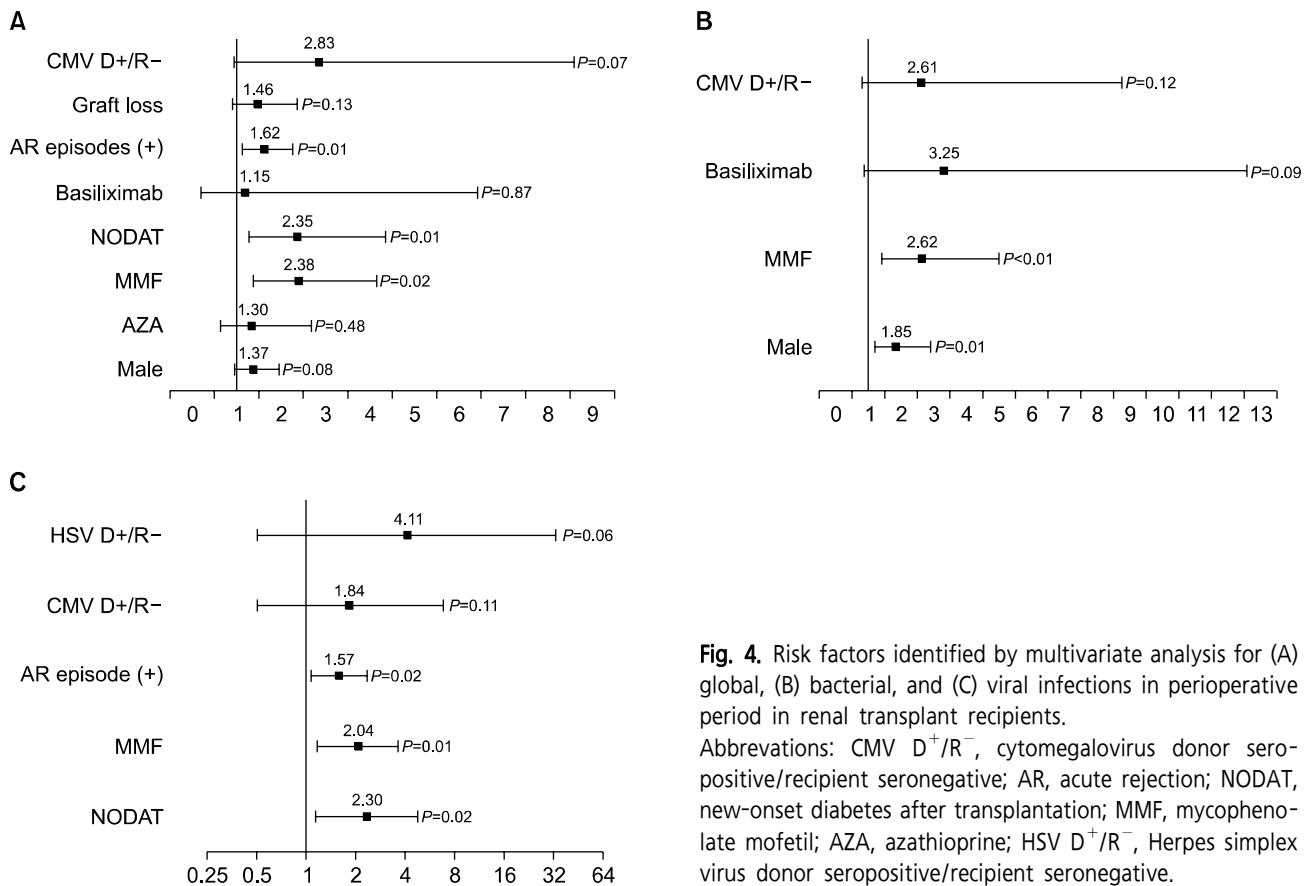


Fig. 4. Risk factors identified by multivariate analysis for (A) global, (B) bacterial, and (C) viral infections in perioperative period in renal transplant recipients.

Abbreviations: CMV D⁺/R⁻, cytomegalovirus donor seropositive/recipient seronegative; AR, acute rejection; NODAT, new-onset diabetes after transplantation; MMF, mycophenolate mofetil; AZA, azathioprine; HSV D⁺/R⁻, Herpes simplex virus donor seropositive/recipient seronegative.

tenance of a balance between rejection and infection.

This study demonstrated a significant reduction in the risk of acute rejection along with an improvement in overall graft survival, consistent with several previous multicenter randomized controlled MMF trials and a recent systematic meta-analysis(16-19). The MMF group had the lowest rate of acute rejection (14.6%) within the 5th post-transplant year compared to the double (28.4%) and AZA (32.1%) groups in the present study, and had the most improved graft- ($P<0.001$) and death-censored graft survival ($P=0.005$). At the same time, immunosuppression without MMF showed higher risk of graft loss in Cox Regression analysis. However, this improvement in graft outcome was achieved at the expense of post-transplant infections in MMF-receiving patients. The real incidence of post-transplant infection adjusted by the time at risk was significantly higher in the MMF group than in the Double or AZA groups during the first post-transplant month ($P=0.01$). The increases in infection risk after introduction of MMF

have also been reported in different study setting. A retrospective cohort study demonstrated that the rate of repeat hospitalization for infection was significantly higher in patients treated with MMF(16); another study revealed that a late MMF introduction and a switch from AZA to MMF treatment resulted in significantly increased infection rates in renal transplant recipients(19).

Infectious complications have been known to occur in a generally predictable pattern and categorized according to the post-transplant time period in which they occur, as previously discussed(15). Postsurgical bacterial infections usually occur in the first month after transplantation; opportunistic infections (particularly cytomegalovirus) are significant at 1 to 6 months post-transplantation; and a mixture of community-acquired and opportunistic infections are usually identified in the late post-transplant period. However, this study clearly showed that viral infection has significantly increased with the clinical use of MMF and became the

most common cause of post-transplant infection within one month after transplantation. An increased incidence of viral infection was independently associated with MMF ($P=0.013$), NODAT ($P=0.022$), and AR episodes ($P=0.021$). The effects of MMF on the recipient susceptibility to viral infection was supported by a recent study which identified a significant association between MMF use and neutropenia frequently associated with a higher incidence of both bacterial and CMV infections(20). Taken together, these results suggested that MMF treatment altered the rate and time of post-transplant infection which was previously discussed by Rubin et al(21) and resulted in viral infections as the most common infections in the first month post-transplantation.

It should be noted that virtually no mismatched CMV donor/recipient pairs were observed in this study as most Korean adults are seropositive for CMV(22). Although the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline indicates patients with CMV serology of D^+/R^+ are at risk for developing CMV infection and chemoprophylaxis is recommended in such kidney transplant recipients(23), no recipients received anti-CMV prophylaxes except for D^+/R^- pairs in this study population. Though the real incidence of viral infection including CMV was higher in the MMF group, the conventional incidence rates were 4.0%, 4.1% and 6.3% at perioperative, early and late post-transplant periods, respectively. Specifically, CMV infection rates were only 0.8%, 2.3% and 3.3% at each period, which is significantly low compared to other studies(24,25). This could be explained by a relatively low dose of MMF (1~1.5 g/day). Indeed, the dose-dependent increased rate of CMV infection in recipients receiving MMF has been well described(26) and neutropenia occurred in recipients with MMF use can be a possible mechanism of this dose-dependent relationship(20).

The results of this study should be interpreted in the context of its limitations. In spite of data collection from prospectively including database, this study was retrospective in nature and patients were not randomized into immunosuppression study groups. One group was clinically managed prior to the other groups. Alth-

ough the transplant era which was divided as 1990~1994, 1995~1999 and 2000~2005 was not associated with graft survival or infectious complications in the multivariate analyses, results may have been biased by unidentified factors that changed over time. Prospective randomized studies with larger cohort size are required to further explore the risks of MMF use in the development of viral infection and to evaluate whether MMF-associated viral infection is dose-dependent.

In summary, MMF significantly reduced the risk of acute rejection and improved overall graft survival in renal transplant recipients in the present study. However, MMF also increased the occurrence of post-transplant infectious complications. Further, most post-transplantation infections were viral in nature in the first post-transplant month. This finding suggests that viral infection is not restricted to second period (1~6 months) infections, and should be considered a primary source of infectious complications immediately after transplantation in MMF-treated recipients. Clinicians should attempt to balance the beneficial effects of MMF therapy (AR reduction) with the detrimental effects (viral infection) in the management of transplant patients.

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