# The Development of Acute Kidney Disease Following Allogeneic Hematopoietic Stem Cell Transplantation

# Allojenik Hematopoetik Kök Hücre Nakli Sonrası Akut Böbrek Hastalığı Gelişimi

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## ÖZET

**GİRİŞ ve AMAÇ**: Akut böbrek hastalığı, allojenik hematopoetik kök hücre naklinin önemli komplikasyonlarından biridir. Bu çalışmada hematopoetik kök hücre naklinde akut böbrek hastalığı için major risk faktörlerini ve bunun hastaların yaşam süresi üzerine olan etkisini değerlendirmeyi amaçladık.

**YÖNTEM ve GEREÇLER:** Bu çalışmada kliniğimizde Ocak 2007 ile Ekim 2015 yılları arasında allojenik hematopoetik kök hücre nakli olan 77 hastayı retrospektif olarak değerlendirdik.

**BULGULAR:** Çalışmaya alınan 77 hastanın 25'inde (%32.5) akut böbrek hastalığı gelişti. Transplantasyondan sonra akut böbrek hastalığının ortalama gelişme süresi 30 gündü. Univariate analizde bazal serum gamma-glutamil transpeptidaz düzeyi, amfoterisin B kullanımı ve özellikle siklosporin düzeyinin akut böbrek hastalığı gelişme riski ile ilişkili olduğu gösterildi. Lojistik regresyon multivariate analizde amfoterisin B kullanımı, sitomegalovirüs reaktivasyonu, hazırlama rejimi ve siklosporin düzeyinin akut böbrek hastalığı için bağımsız risk faktörleri olduğu tespit edildi. Mortalite ve non-relaps mortalite oranları akut böbrek hastalığı olan hastalarda, akut böbrek hastalığı olmayan hastalara göre daha yüksekti. Kaplan-Meier analizde, ortalama yaşam süresi akut böbrek hastalığı olmayan hastalarda 18.4 ay iken, akut böbrek hastalığı olan hastalarda 12.2 aydı.

**TARTIŞMA ve SONUÇ:** Akut böbrek hastalığı, hematopoetik kök hücre naklinde kötü prognoza sahiptir ve hazırlama rejimi, sitomegalovirüs reaktivasyonu, amfoterisin B kullanımı ve özellikle siklosporin düzeyi hematopoetik kök hücre nakil alıcılarında akut böbrek hastalığı gelişmesi için bağımsız risk faktörü olarak göz önünde bulundurulmalıdır.

**Anahtar Kelimeler:** Allojenik hematopoetik kök hücre nakli, Akut böbrek hastalığı, Siklosporin, Amfoterisin B, Mortalite

## ABSTRACT

**INTRODUCTION:** Acute kidney disease is an important complication of allogeneic hematopoietic stem cell transplantation. The aim of this retrospective study was to identify major risk factors for acute kidney disease in hematopoietic stem cell transplantation and its effect on patients survival.

**METHODS:** This study was a retrospective review of 77 patients with allogeneic hematopoietic stem cell transplantation at our department from January 2007 to October 2015.

**RESULTS:** Acute kidney disease developed in 25 of 77 patients (32.5%). The median time to development of acute kidney disease after transplantation was 30 days. Univariate analysis showed that baseline serum gamma-glutamyl transpeptidase level, amphotericin B use and cyclosporine level were associated with the development of acute kidney disease. Logistic regression multivariate analysis showed that amphotericin B use, cytomegalovirus reactivation, conditioning regimen and cyclosporine level were an independent risk factor for

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acute kidney disease. Mortality and non-relapse mortality rates were higher in patients with acute kidney disease than in those without acute kidney disease. In Kaplan-Meier analysis, median survival was 18.4 months in patients without acute kidney disease and 12.2 months in patients with acute kidney disease.
**DISCUSSION and CONCLUSION:** Acute kidney disease has a poor prognosis in hematopoietic stem cell transplantation and conditioning regimen, cytomegalovirus reactivation, amphotericin B use and particularly cyclosporine level are independent risk factors in the development of acute kidney disease in hematopoietic stem cell transplantation recipients.
**Keywords:** Allogeneic hematopoietic stem cell transplantation, Acute kidney disease, Cyclosporine, Amphotericin B, Mortality

## INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is an effective treatment method for hematological diseases such as acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), myelodysplastic syndrome (MDS) and lymphoma. However, treatment-related toxicity such as acute kidney disease (AKD) limits the success of HSCT (1,2). Mortality rate is three times higher in patients developing AKD following HSCT. Moreover, it is 80% or higher in subjects requiring dialysis (3). Graft-versus-host disease (GVHD), veno-occlusive disease (VOD), bacterial and fungal infections, cyclosporine, amphotericin B and/or aminoglycoside antibiotics use have been shown to be associated with AKD in HSCT recipients (4). Especially, since cyclosporine presents a narrow therapeutic index, it is an important risk factor for AKD (5,6). Cyclosporine causes vasoconstriction in renal afferent arterioles by increasing vasoconstrictor agents such as endothelin and thromboxane and decreasing vasodilator agents such as prostaglandin $E_2$, prostacyclin and nitric oxide. Consequently, it leads to tubular injury and acute reversible renal dysfunction (7).

The aim of this retrospective study was to identify major risk factors for AKD in HSCT and its effect on patients survival.

## MATERIALS and METHODS

### *Patients*

Clinical data were analyzed retrospectively in 77 adult patients who received HSCT at the Karadeniz Technical University, Faculty of Medicine, Department of Hematology between January 2007 and October 2015. All patients received hematopoietic stem cells from HLA-matched related donors. Patient data were collected and analyzed retrospectively using a database and the hospital patient record system. The study was approved by the research ethics committee of the Karadeniz Technical University. All patients were informed about the study.

### *Stem Cell Transplantation Procedure*

The myeloablative (MA) - conditioning regimen consisted of busulfan (0.8 mg/kg/day, once every 6 hours for 4 days, iv) and cyclophosphamide (60 mg/kg/day for 2 days, iv). The non-MA (NMA) - conditioning regimen consisted of fludarabine (30 $mg/m^2$/day for 6 days, iv), busulfan (0.8 mg/kg/day, once every 6 hours for 2 days, iv) and antithymocyte globulin (rabbit ATG) (5 mg/kg/day for 4 days, iv). Graft was injected on day 0 after the end of chemotherapy. All patients were given cyclosporine and short-term methotrexate for GVHD prophylaxis. Cyclosporine was started at 3 mg/kg/day on day -2 in patients receiving the MA - conditioning regimen and at 3 mg/kg/day on day -1 in patients receiving the non-MA - conditioning regimen by continuous infusion and was maintained until modification to the oral route. Serum cyclosporine and creatinine levels were measured at least twice a week in the first month and once a week subsequently until cyclosporine was discontinued. Serum cyclosporine level was adjusted to maintain the blood concentration of 200 - 400 ng/mL depending on serum bilirubin and creatinine levels.

Infection prophylaxis consisted of ciprofloxacin (500 mg/day, twice daily from day -5 to discharge, po), fluconazole (200 mg/day, twice daily from day +1 to +100, po) and acyclovir (600 mg/day, three times daily from day -4 to +30, po).

### *Measurements and Definitions*

Data on patient characteristics were collected during transplantation, and age, gender, underlying disease, disease risk, conditioning

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regimen and hypertension before transplantation were recorded. The following posttransplant complications (when they emerged in the first 3 months of transplantation) such as GVHD, cytomegalovirus (CMV) reactivation and amphotericin B use were also noted.

Baseline serum creatinine, baseline serum blood urea nitrogen (BUN), baseline serum potassium, baseline serum magnesium, baseline serum aspartate aminotransferase (AST), baseline serum alanine aminotransferase (ALT), baseline serum gamma-glutamyl transpeptidase (GGT), baseline serum alkaline phosphatase (ALP) and baseline serum direct bilirubin levels before conditioning regimen were examined. Glomerular filtration rate (GFR) was calculated using the MDRD formula (GFR mL/min per 1.73 $m^2$ = 186.3 × serum creatinine $^{-1.154}$ × age$^{-0.203}$ × (0.742 for female)) based on the highest serum creatinine level in the first 3 months posttransplantation (8). AKD was defined as 2-fold increase in creatinine level within 3 months after transplantation. AKD was classified according to KDIGO AKD classification (9). Additionally, mean cyclosporine level was calculated based on four cyclosporine levels before the highest serum creatinine level.

Hypertension before transplantation was defined as a documented history of hypertension or antihypertensive drug use.

GVHD was diagnosed and staged according to the current grading system (10).

CMV reactivation was defined as DNA > 500 copies/mL in two consecutive titers.

Patients with acute leukemia in first complete remission, low-risk MDS, aplastic anemia and lymphoma in first or second complete remission were considered low risk and others were considered high risk.

***Statistical Analysis***

Statistical analysis was performed on SPSS version 23 software. Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were calculated as median and percentage quartiles. The Kolmogorov-Smirnov test was used to determine data distribution. Qualitative data were compared with the Chi-square test. The Student-*t* test was used in the comparison of normally distributed data and the Mann-Whitney *U* test was used for nonnormally distributed data. Multivariate logistic regression analysis was performed to examine the relative contributions of parameters on the outcome of AKD. Survival was analyzed by the Kaplan-Meier method. $P < 0.05$ was considered statistically significant.

## RESULTS

***Patients Characteristics***

Thirty-one female and 46 male, with a mean age of 40.6 ± 12.7 years, were studied. MA HSCT was performed in 50 patients and NMA HSCT in 27 patients. No patients had renal dysfunction before transplantation. GVHD developed in 32 patients (41.6%) and CMV reactivation in 29 patients (37.7%). The baseline characteristics and posttransplantation complications of the patients included in the study are shown in Table 1.

***AKD: Incidence and Risk Factors***

AKD developed in 25 of 77 patients (32.5%). AKD developed in 19 of 50 patients (38%) undergoing MA HSCT and in 6 of 27 patients (22%) undergoing NMA HSCT. The highest creatinine level was 2.2 mg/dL (1.7-2.5), the highest BUN level was 30 ± 16.5 mg/dL and the lowest GFR was 34 mL/min/1.73$m^2$ (25.5-45.5). The median time to development of AKD after transplantation was 30 days (range 9-71 days). One patient required dialysis. The median time to improvement of AKD was 24 days (range 4-137 days).

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**Table 1.** Baseline Characteristics and Posttransplant Complications of Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

| **Characteristics** | **Value (n: 77)** |
|---|---|
| Age (years) mean ± SD | 40.6 ± 12.7 |
| Gender (female/male) n, (%) | 31 (40.3%) / 46 (59.7%) |
| Conditioning regimen (MA/NMA) n, (%) | 50 (64.9%) / 27 (35.1%) |
| Disease risk (standard/high) n, (%) | 59 (76.6%) / 18 (23.4%) |
| Underlying disease n, (%) | |
| Acute myeloid leukemia | 40 (51.9%) |
| Acute lymphocytic leukemia | 18 (23.4%) |
| Myelodysplastic syndrome | 7 (9.1%) |
| Lymphoma | 5 (6.5%) |
| Aplastic anemia | 3 (3.9%) |
| Myelofibrosis | 2 (2.6%) |
| Chronic myelomonocytic leukemia | 2 (2.6%) |
| Hypertension before transplantation n, (%) | 6 (7.8%) |
| Baseline serum creatinine (mg/dL) median (range) | 0.7 (0.5-0.8) |
| Baseline serum BUN (mg/dL) mean ± SD | 12.4 ± 4 |
| Baseline GFR (mL/min/1.73m$^2$) median (range) | 131 (102-158.5) |
| Baseline serum potassium ( mEq/L) mean ± SD | 4 ± 0.4 |
| Baseline serum magnesium (mg/dL) median (range) | 1.9 (1.85-2) |
| Cyclosporine (ng/mL) mean ± SD | 316 ± 100.7 |
| Baseline serum AST (U/L) median (range) | 22 (16-33) |
| Baseline serum ALT (U/L) median (range) | 30 (14.5-51) |
| Baseline serum GGT (U/L) median (range) | 29 (18-61) |
| Baseline serum ALP (U/L) median (range) | 87 (73-108) |
| Baseline serum direct bilirubin (mg/dL) median (range) | 0.1 (0.1-0.2) |
| Amphotericin B n, (%) | 19 (24.7%) |
| CMV reactivation n, (%) | 29 (37.7%) |
| Graft-versus-host disease n, (%) | 32 (41.6%) |

SD, standard deviation; MA, myeloablative; NMA, non-myeloablative; BUN, blood urea nitrogen; GFR, glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; CMV, cytomegalovirus.

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**Table 2.** Univariate Analysis of Risk Factors for Acute Kidney Disease

| Risk Factors | No ARF (n:52) | ARF (n:25) | P value |
|---|---|---|---|
| Age (years) mean ± SD | 41.2 (±13) | 39.5 (±12.5) | 0.6 |
| Gender n, (%) | | | |
| Female | 23 (44.2%) | 8 (32%) | 0.4 |
| Male | 29 (55.8%) | 17 (68%) | |
| Conditioning regimen n, (%) | | | |
| MA | 31 (59.6%) | 19 (76%) | 0.2 |
| NMA | 21 (40.4%) | 6 (24%) | |
| Disease risk n, (%) | | | |
| Standard | 40 (76.9%) | 19 (76%) | 1 |
| High | 12 (23.1%) | 6 (24%) | |
| Underlying disease n, (%) | | | |
| Acute myeloid leukemia | 31 (59.6%) | 9 (36%) | 0.1 |
| Acute lymphocytic leukemia | 9 (17.3%) | 9 (36%) | |
| Other diseases | 12 (23.1%) | 7 (28%) | |
| Hypertension before transplantation n, (%) | 4 (7.7%) | 2 (8%) | 1 |
| Baseline serum creatinine (mg/dL) median (range) | 0.7 (0.5-0.7) | 0.8 (0.5-0.9) | 0.1 |
| Baseline serum BUN (mg/dL) mean ± SD | 12.1 ± 4.2 | 13 ± 3.6 | 0.4 |
| Baseline GFR (mL/min/1.73m$^2$) median (range) | 134 (104.5-152) | 112 (92-167.5) | 0.3 |
| Baseline serum potassium ( mEq/L) mean ± SD | 4.1 ± 0.5 | 4 ± 0.3 | 0.6 |
| Baseline serum magnesium (mg/dL) median (range) | 2 (1.8-2) | 1.9 (1.9-2) | 0.6 |
| Cyclosporine (ng/mL) mean ± SD | 316 ± 100.7 | 400.9 ± 96.3 | 0.001 |
| Baseline serum AST (U/L) median (range) | 21(14.2-31.5) | 27 (27 (18.5-36) | 0.08 |
| Baseline serum ALT (U/L) median (range) | 25.5 (13-48.5) | 37 (20-60) | 0.06 |
| Baseline serum GGT (U/L) median (range) | 24 (16.2-54.2) | 37 (27.5-79) | 0.01 |
| Baseline serum ALP (U/L) median (range) | 87 (73-128.5) | 85 (74.5-94.5) | 0.6 |
| Baseline serum direct bilirubin (mg/dL) median (range) | 0.1 (0.1-0.2) | 0.1 (0.1-0.15) | 0.7 |
| Amphotericin B n, (%) | 8 (15.4%) | 11 (44%) | 0.01 |
| CMV reactivation n, (%) | 16 (30.8%) | 13 (52%) | 0.1 |
| Graft-versus-host disease n, (%) | 20 (38.5%) | 12 (48%) | 0.5 |

SD, standard deviation; MA, myeloablative; NMA, non-myeloablative; BUN, blood urea nitrogen; GFR, glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; CMV, cytomegalovirus.

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**Table 3.** Multivariate Analysis of Risk Factors for Acute Kidney Disease

| Risk Factors | OR %95 CI | P-value |
|---|---|---|
| Amphotericin B | OR 7.6 95% CI 1.781-32.395 | 0.006 |
| CMV reactivation | OR 3.7 95% CI 1.027-13.350 | 0.04 |
| Conditioning regimen | OR 5.5 95% CI 1.152-25.909 | 0.03 |
| Cyclosporine | OR 1 95% CI 1.006-1.021 | 0.001 |

OR, odds ratio; CI, confidence interval; CMV, cytomegalovirus

**Table 4.** The survival according to the stages of KDIGO

| KDIGO | Patients no (n) | OR %95 CI | P-value |
|---|---|---|---|
| Stage 1 | 3 | OR 5.6 95% CI 3.626-7.574 | >0.05 |
| Stage 2 | 10 | OR 8.4 95% CI 0-31.056 | |
| Stage 3 | 12 | OR 12.2 95% CI 0-32.705 | |

OR, odds ratio; CI, confidence interval

There was no statistical difference for AKD in age, gender, disease risk, underlying disease, hypertension before transplantation, baseline serum creatinine, baseline serum BUN, baseline serum potassium, baseline serum magnesium, baseline serum AST or baseline serum ALP levels. Univariate analysis showed that baseline serum GGT level, amphotericin B use and cyclosporine level were associated with the development of AKD. Baseline serum ALT (borderline significant) and baseline serum GGT levels were higher in patients with AKD compared to those without AKD (37 U/L, 95% CI 31.93-60.95; 25.5 U/L, 95% CI 26.42-42.58, p= 0.06, and 37 U/L, 95% CI 38.93-76.75; 24 U/L, 95% CI 29.42-82.78, p = 0.01, respectively). The incidence of AKD in patients with amphotericin B use was significantly higher than in patients without amphotericin B use (44%, 95% CI 24-64; 15.4%, 95% CI 5.8-25, p=0.01, respectively). Cyclosporine level was higher in patients with AKD compared to those without AKD (400.9 ± 96.3 ng/mL, 95% CI 361.21-440.71; 316 ± 100.7 ng/mL, 95% CI 288.09-344.14, p=0.001, respectively). AKD developed in 5 of 28 patients with cyclosporine level < 300 ng/mL (17.9%, 95% CI 3.7-32.1) and in 20 of 49 patients with level ≥ 300 ng/mL (40.8%, 95% CI 28.6-55.1), and this was statistically borderline significant (p=0.06). There was no statistical difference for AKD in CMV reactivation or GVHD after transplantation (Table 2). No significant difference was observed for cyclosporine level in patients with GVHD compared to those without GVHD (317 ng/mL, 363 ng/mL, respectively, p>0.05).

Logistic regression multivariate analysis showed that amphotericin B use, CMV reactivation, conditioning regimen and cyclosporine level were an independent risk factor for AKD (OR 7.6 95% CI 1.781-32.395, p=0.006; OR 3.7 95% CI 1.027-13.350, p=0.04; OR 5.5 95% CI 1.152-25.909, p=0.03; OR 1 95% CI 1.006-1.021, p=0.001, respectively) (Table 3).

***Patient Survival Analysis***

Fifty-five (71.4%) of 77 patients died and 22 (28.6%) survived. Causes of death included relapse in 25 patients (45.4%), GVHD in 9 patients (16.7%), pneumonia in 4 patients (7.2%), graft failure in 4 patients (7.2%), fungal infection in 3 patients (5.4%), intracranial hemorrhage in 3 patients (5.4%), sepsis in 1 patient (1.8%), gall bladder perforation in 1 patient (1.8%) and unknown causes in 5 patients (9.1%). No statistically significant difference was observed in terms of relapse between patients with or without AKD. Mortality and non-relapse mortality rates were higher in patients with AKD than in those without AKD (p=0.01, p=0.05, respectively). In Kaplan-Meier analysis, median survival was 18.4 months in patients without AKD and 12.2 months in patients with AKD and differed significantly among groups (95% CI 7.6-29.2;

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95% CI 0-31, p=0.01, respectively) (Figure 1). But, there was no significant difference for mortality between stage 1, stage 2 and stage 3 AKD according to KDIGO classification (p>0.05) (Table 4). Median survival was 5.6 months in patients with stage 1 AKD, 8.4 months in patients with stage 2 AKD and 12.2 months in patients with stage 3 AKD.

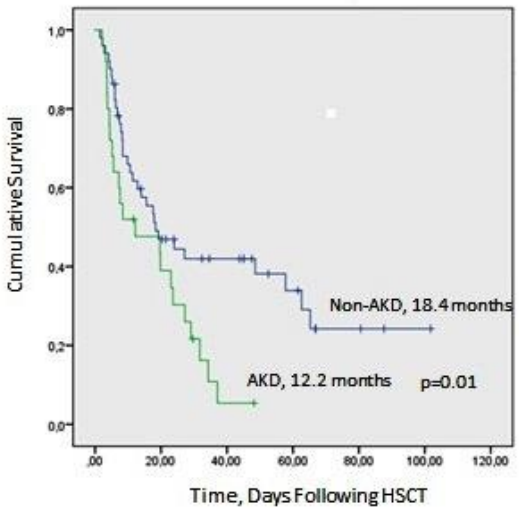


**Figure 1.** Kaplan-Maier Survival Curve of AKD and Non-AKD After Allogeneic Hematopoietic Stem Cell Transplantation

## DISCUSSION

AKD is one of the major complications of HSCT. Previous studies reported that the incidence of AKD during transplantation ranged from 17% and 73%. Even this condition is as high as 90% in some studies (11,12). In our study, AKD developed in 32.5% of patients. Although, in the literature, the median time to onset of AKD after HSCT was between 14 and 21 days, it was 30 days in this study (13). VOD is an important risk factor for the development of AKD. Besides, in patients with VOD, Helal et al. reported that acute renal failure developed significantly shorter time after HSCT (14). In this study, AKD was very later and less as compared to in previous studies, this may be because of the low frequency of VOD. Portal hypertension resulting from VOD leads to both decreased renal perfusion and tubular injury. A study showed that the presence of VOD and increased total bilirubin was associated with increased risk of AKD (15). In our study, only one patient had VOD, therefore we are unable to comparison between VOD and AKD.

We analyzed the relation between patient characteristics at the time of transplantation and the development of AKD. No association was determined between the development of AKD and age, gender, disease risk, underlying disease, hypertension before transplantation, baseline serum creatinine, baseline serum BUN, baseline GFR, baseline serum potassium, baseline serum magnesium levels. MA conditioning regimen causes more frequent organ toxicity. Various studies have been reported that AKD occurs in 36-80% after MA HSCT and in 33-56% after NMA HSCT (2,16,17). In our study, AKD developed in 38% of patients receiving MA HSCT and 22% of patients receiving NMA HSCT. MA HSCT was also identified as an independent risk factor for AKD at multivariate analysis.

One mouse study showed severe infiltration of cytotoxic T lymphocyte in the kidneys during GVHD and renal failure was thought to develop in association with cytokine and immune-related injury. Nephrotoxic drug use and dehydration also contribute to the development of AKD in GVHD (18,19). Pinana et al. showed that AKD was more common in patients receiving NMA HSCT developing GVHD (20). However, in contrast to previous studies, we observed no association between GVHD and AKD. This may be because there was no increase in the level of cyclosporine in patients with GVHD in our study. On the other hand, the number of studies reporting an association between CMV reactivation, a significant complication of HSCT, and AKD is also limited. In the present study, multivariate analysis showed that CMV reactivation is an independent risk factor for AKD in HSCT patients. Immune damage or medications after CMV infection may also consider the development of AKD (21).

Cyclosporine is an important risk factor in the development of nephrotoxicity in HSCT recipients. In particular, continuous usage and increasing serum level of cyclosporine trigger nephrotoxicity (22,23). Kennedy et al. reported that the development of nephrotoxicity was higher and faster in patients with cyclosporine level above 250 ng/mL compared to those with below 150 ng/mL (23). Another study showed that

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cyclosporine was approximately six times higher risk factor for AKD (24). In our study, cyclosporine level was significantly higher in patients with AKD than in those without AKD. Moreover, AKD was more common in patients with cyclosporine level above 300 ng/mL. In addition, cyclosporine was identified as an independent risk factor for AKD in multivariate analysis. Additionally in our study, baseline ALT and particularly GGT levels were higher in patients developing AKD. Since cyclosporine is a drug metabolized via the cytochrome P450 system, the impairment of liver function tests can compromise elimination of the drug and result in an increase in cyclosporine level. In addition, the use together with cyclosporine of nephrotoxic agents such as amphotericin B and/or aminoglycoside exhibits a toxic synergistic effect for AKD (16,22,24). Saddani et al. showed that amphotericin B use is an independent risk factor for AKD in HSCT patients (24). It is well know that cyclosporine and amphotericin B may lead to acute tubular necrosis (11). In this study, amphotericin B was applied in 24.7% of patients and amphotericin B use was higher in patients developing AKD. Besides, amphotericin B was also identified as an independent risk factor for AKD in multivariate analysis. We considered that cyclosporine caused nephrotoxicity by both in a dose-dependent toxicity and synergistic effect with amphotericin B.

AKD is associated with increased mortality and reduced survival in HSCT patients (25). The mechanism is uncertain, but it is responsible from some factors such as volume overload, coagulation abnormalities, multiorgan failure, sepsis and cytokine or immune-related organ injury. In addition, since AKD affects the dose of calcineurin inhibitors, it may also increase mortality by causing GVHD (1). Similarly in this study, total mortality and non-relapse mortality rates were higher in patients with AKD. A study showed that mortality rates of patients increased with the rise in severity of AKD categories according to RIFLE criteria (15). Also, in another study, survival rates were higher in patients with grade 0 and grade 1 AKD compared to patients with grade 2 and grade 3 AKD (12). Unlike, there was no significant difference for mortality between stage 1, stage 2 and stage 3 AKD in our study. This may be due to the small number of patients with AKD.

## Conclusion

We think that conditioning regimen, CMV reactivation, amphotericin B use and particularly cyclosporine level are independent risk factors in the development of AKD in HSCT recipients. Additionally, AKD has a poor prognosis in HSCT recipients. The strategy to investigate and prevent possible risk factors for nephrotoxicity would be imperative to improve survival in HSCT patients.

### *Conflicts of interest*

The authors declare no conflicts of interest

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