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黒川, 麻里

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Title Hyperferritinemia and acute kidney injury in pediatric patients receiving allogeneic hematopoietic cell transplantation

Authors Mari Kurokawa, MD[1], Kei Nishiyama, MD[1], Yuhki Koga, MD, PhD[1], Katsuhide Eguchi, MD[1], Takashi Imai, MD, PhD[1], Utako Oba, MD[1], Akira Shiraishi, MD, PhD[1], Hazumu Nagata, MD, PhD[1], Noriyuki Kaku, MD, PhD[1,2], Masataka Ishimura, MD, PhD[1], Satoshi Honjo, MD, PhD[3], Shouichi Ohga, MD, PhD[1]

Affiliations 1. Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan. 2. Pediatric Intensive Care Unit, Kyushu University Hospital, Fukuoka, Japan. 3. Department of Pediatrics, National Hospital Organization Fukuoka National Hospital, Fukuoka, Japan.

Corresponding author Yuhki Koga, MD, PhD, yuuki-k@pediatr.med.kyushu-u.ac.jp

Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. TEL: +81-92-642-5421, FAX: +81-92-642-5435,

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6

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8 taking primary responsibility for the paper. KE, TI, UO, AS, and MI performed the
9 clinical management with helpful discussion regarding the completion of the work. HN
10 and NK conducted critical care. SH gave advice on the statistical analyses.

11

12 **Abbreviations** AKI, acute kidney injury; HCT, hematopoietic cell transplantation;
13 OS, overall survival; HR, hazard ratio; CI, confidence interval; HLA, human leukocyte
14 antigen; TBI, total body irradiation; VOD, veno-occlusive disease; GVHD, graft-versus-
15 host disease; CMV, cytomegalovirus; SOS, sinusoidal obstruction syndrome.

16

Abstract

Introduction Acute kidney injury (AKI) often occurs in pediatric patients who received allogeneic hematopoietic cell transplantation (HCT). We evaluated the risk and effect of HCT-related AKI in pediatric patients.

Methods We retrospectively studied the survival and renal outcome of 69 children 100 days and 1-year posttransplant in our institution in 2004-2016. Stage-3 AKI developed in 34 patients (49%) until 100 days posttransplant.

Results The 100-day overall survival (OS) rates of patients with stage-3 AKI were lower than those without it (76.5% *vs.* 94.3%, *P*=0.035). The 1-year OS rates did not differ markedly between 21 post-100-day survivors with stage-3 AKI and 29 without it (80.8% *vs.* 87.9%, *P*=0.444). The causes of 19 deaths included the relapse of underlying disease or graft failure (n=11), treatment-related events (4), and second HCT-related events (4). Underlying disease of malignancy (crude hazard ratio [HR] 5.7; 95% confidence interval [CI], 2.20 to 14.96), >1000 ng/ml ferritinemia (crude HR 4.29; 95% CI, 2.11 to 8.71), stem cell source of peripheral (crude HR 2.96; 95% CI, 1.22 to 7.20) or cord blood (crude HR 2.29; 95% CI, 1.03 to 5.06), and myeloablative regimen (crude HR 2.56; 95% CI, 1.24 to 5.26) were identified as risk factors for stage-3 AKI until 100 days posttransplant. Hyperferritinemia alone was significant (adjusted HR 5.52; 95% CI, 2.21 to 13.76) on multivariable analyses.

Conclusions Hyperferritinemia was associated with stage-3 AKI and early mortality posttransplant. Pretransplant iron control may protect the kidney of pediatric HCT-survivors.

Introduction

Hematopoietic cell transplantation (HCT) is a curative treatment for hematologic malignancies and non-malignant disorders, including bone marrow failure syndromes, primary immunodeficiency diseases, inborn errors of metabolism, and autoimmune or autoinflammatory disorders. As the number of HCT procedures has been increasing globally [1], late effects have become a substantial burden for survivors [2]. Despite progress in the management of HCT, acute kidney injury (AKI) remains a grave complication during and after HCT. Although the definition of AKI differs among studies, the estimated incidence following pediatric allogeneic HCT has been reported to be 21% to 53% when defined as the doubling of the baseline serum creatinine level up to 3 months posttransplant [3-7].

Many HCT candidates have an increased risk of AKI or substantial renal disease due to prior therapy- or underlying disease-associated factors. The conditioning and complication of HCT further raises the risk of renal damage in these patients. Each patient also has an individual background risk, depending on the underlying disease, history of therapy, and coexisting inflammation and infection. The reported risk factors for AKI in patients after HCT are recipient-related factors (older age, history of AKI, and a reduced initial GFR), HCT-related factors (allogeneic HCT, human leukocyte antigen [HLA]-disparate related donor, unrelated donor, total body irradiation [TBI], and myeloablative conditioning), nephrotoxic drugs (cyclophosphamide, etoposide, amphotericin B, aminoglycosides, foscarnet, spironolactone, and calcineurin inhibitors), and HCT-associated complications (sepsis, hyperbilirubinemia, veno-occlusive disease [VOD], grade III-IV graft-versus-host disease [GVHD], and thrombotic

microangiopathy) [6-9]. Iron overload is also reported to be a significant contributor to treatment-related mortality among patients with HCT [10-12]. When glomerular and renal tubular cells are exposed to a high concentration of iron and iron-containing proteins, increased levels of intracellular catalytic iron may precipitate renal damage [13]. However, there is little information about the association between iron overload and the development of AKI in patients after HCT.

AKI is associated with the mortality and morbidity of chronic kidney disease in both pediatric and adult transplant survivors [3,8, 14, 15]. Stage-3 AKI has a substantial impact on the mortality rate of patients after HCT. However, the direct effects of AKI on the outcomes of posttransplant patients are controversial. The cause of death in AKI patients was not related to renal failure in two previous reports [4-6]. However, fluid overload is known to carry a risk of acute death in patients with AKI after HCT [16]. Neither the early nor late effects of AKI on the mortality and morbidity of pediatric patients after HCT have been clarified.

To assess the risk and effect of HCT-related AKI, we retrospectively analyzed the survival and renal outcomes of 69 pediatric patients who received allogeneic HCT in our institution between 2004 and 2016. First, we studied the risk of developing stage-3 AKI within 100 days after HCT with respect to the aforementioned variables focusing on serum ferritin levels. Next, the overall survival (OS) rates were compared between patients with and without stage-3 AKI in the early (0-100 days after HCT) and late period (101-365 days after HCT). Finally, we investigated the causes of death and AKI in these two periods.

Methods

Patients

This study included 115 patients who consecutively received first allogeneic HCT from January 2004 to October 2016 at Department of Pediatrics in Kyushu University Hospital. Estimated GFR before the conditioning regimen was calculated using the creatinine-based equation to estimate the glomerular filtration rate in Japanese children and adolescents [17]. We excluded 39 patients under 2 and over 19 years of age who were not suited for coverage with this equation. Seven patients with an estimated GFR <90 ml/min/m^2 before HCT were excluded. A total of 69 patients were therefore enrolled in this study (**Figure 1**).

The following information was collected from the medical records: sex, age at HCT, underlying disease, serum ferritin levels before HCT, donor type, donor cell source, HLA matching, conditioning regimen, and dose of TBI. To eliminate the effect of acute infections, serum ferritin levels were assessed at the time of the pre-transplant phase free from infection. Posttransplant information was collected for serum creatinine levels, the survival, cause of death, relapse, graft failure, second HCT, acute GVHD, cytomegalovirus (CMV) infection, BK virus infection, and bacteremia. This study was certified by the Institutional Review Board of Kyushu University (2019-252).

Definitions

AKI within the first 100 days after transplantation was graded according to the AKI network classification system, which was modified from its original version [18]. Stage-

1, stage-2, and stage-3 AKI were defined as a 1.5- to 2.0-fold, >2- to 3-fold, and >3-fold increment in the serum creatinine concentration from the baseline level, respectively. Urine output data were excluded when defining AKI because the posttransplant urine volume was not precisely obtained. The need for renal replacement therapy with hemodialysis or peritoneal dialysis was set to indicate stage-3 AKI. To evaluate the effect of the severity of AKI on the outcomes, we defined the maximum stage of AKI as the highest stage observed within the first 100 days after HCT. Conditioning regimens were defined as myeloablative when they contained ≥ 9 mg/kg busulfan or ≥ 8 Gy fractionated TBI [19]. Acute GVHD was graded according to standard criteria [20].

Statistical analyses

The OS within 100 days after HCT was estimated using Kaplan-Meier methods. The OS at 101-365 days posttransplant was similarly estimated in 59 patients who were alive at 100 days. The survival curves of patients with and without stage-3 AKI were statistically compared using log-rank tests. A Cox regression analysis was used to examine the influence of variables on the occurrence of stage-3 AKI within 100 days after HCT. Cases of death or second HCT were censored.

The patient characteristics included the sex, age at HCT, underlying disease (malignant *vs.* nonmalignant), and serum ferritin level before HCT (≤1000 ng/mL *vs.* >1000 ng/mL). Transplant information included the donor type (related *vs.* unrelated), donor cell source (bone marrow *vs.* peripheral blood/cord blood), HLA matching (mismatched *vs.* matched), conditioning regimen (myeloablative *vs.* reduced intensity), and TBI dose (0 to 4 Gy *vs.* 5 to 12 Gy). HCT complications included the GVHD

severity (grade 0 or I *vs.* grade II/grade III or IV), CMV infection, BK virus infection, and bacteremia. The contribution of calcineurin inhibitors (tacrolimus or cyclosporine) was not evaluated because they were used for all patients as a GVHD prophylaxis agent.

In the multivariable analysis, we incorporated variables with the crude hazard ratio that significantly predicted stage-3 AKI, as shown below, as well as factors we assumed were clinically important factors. We performed this Cox regression analysis both with and without backward stepwise selection; the full model included the sex, age at HCT, underlying disease, serum ferritin level before HCT, donor type, donor cell source, HLA matching, conditioning regimen, TBI, GVHD grade, CMV infection, BK virus infection, and bacteremia. First, the full model was fitted, and the least-significant term with $P \geq 0.1$ was removed. The model was then re-estimated, and the least-significant term with $P \geq 0.1$ was removed again. Second, if the most-significant excluded term had $P < 0.05$, that term was entered into the model. These estimation-removing and estimation-adding procedures were repeatedly performed until neither was possible. Finally, the age, sex, and all the clinical covariates mentioned above were entered into the Cox regression model, and backward stepwise selection was performed to examine the robustness of the findings.

Statistical analyses were performed with the JMP software program, version 14 (SAS Institute, Inc., Cary, NC, USA) and the Stata software program, version 14.2 (Stata Corp., College Station, TX, USA). *P* values less than 0.05 were considered to be significant unless otherwise specified.

Results

Patient characteristics

The demographics and clinical profiles of 69 patients who received allo-HCT are shown in **Table 1**. This cohort was 64% male and 36% female. The median age at the time of transplant was 8.4 years old, ranging from 2.1 to 17.7 years old. There were 27 and 42 patients with non-malignant and malignant disease, respectively. The detailed diagnoses for HCT were as follows: (non-malignant diseases) 2 patients with chronic granulomatous disease, 5 aplastic anemia, 7 myelodysplastic syndrome, 4 Wiskott-Aldrich syndrome, 2 chronic active Epstein-Barr virus infection, 3 hemophagocytic syndrome, and 4 other immune deficiency disorders; (malignant diseases) 14 patients with acute lymphoblastic leukemia, 15 acute myeloid leukemia, 3 malignant lymphoma, 7 other leukemia (3 mixed phenotype acute leukemia, 1 acute unclassified leukemia, 1 blastic plasmacytoid dendritic cell neoplasm, 1 granulocytic sarcoma, 1 mature T-cell and NK-cell neoplasm), 2 neuroblastoma, and 1 rhabdomyosarcoma.

The conditioning regimen used differed according to the diagnosis and the stage of the underlying disease. Thirty-four patients received reduced-intensity conditioning, and 35 received myeloablative conditioning regimens. All patients had a fever and neutropenia necessitating, treatment with broad-spectrum antibiotics. Twenty-eight patients (41%) developed grade II or more severe acute GVHD. Twenty (29%), 8 (12%), and 5 patients (7%) received a diagnosis of CMV infection, BK virus infection, and bacteremia, respectively.

Incidence of AKI after allo-HCT

The 100-day cumulative incidences of stage-1, stage-2, and stage-3 AKI, were 14.6%, 15.3%, and 50.7% respectively. The median time to the development of stage-3 AKI was 34.8 days posttransplant, with a range of 7–97 days.

Effects of AKI within 100 days after allo-HCT on OS

The 100-day OS rate of the 34 patients who developed stage-3 AKI was significantly lower than that of the 35 patients who did not (median±SE%, 76.5±7.3% *vs.* 94.3±3.9%, *P*=0.035; **Figure 2A**). In contrast, from 100 days to 365 days, the OS rates did not differ markedly between the 26 patients who developed stage-3 AKI and the 33 who did not (*P*=0.444; **Figure 2B**). Ten and 9 patients died during the early and late periods, respectively (**Supplementary figure**). The proportion of stage-3 AKI in the deceased patients did not significantly differ between the early (8/10) and late (5/9) periods (80% *vs.* 56%, *P*=0.350). The causes of the 10 deaths during the early period were treatment-related mortality in 2 (1 GVHD and 1 sepsis), relapse or graft failure in 7, and death after second HCT in 1. The causes of the nine deaths during the late period were treatment-related mortality in two (sepsis), relapse or graft failure in four, and death after second HCT in three. Most deaths were caused by relapse or graft failure over the first year posttransplant.

Among the 69 patients, 21 developed relapse or graft failure within 1 year after first HCT, and 8 of them underwent second transplantation. After second HCT, the

proportion of patients who developed stage-3 AKI was less than that of patients who did not (25% *vs.* 75%, *P*=0.001; **Supplementary table 1**).

Risk factors for AKI

Table 1 also shows the clinical data for all patients, those who developed stage-3 AKI (n=34), and those who did not (n=35). As shown in this table, underlying disease of malignancy, ferritin level >1000 ng/mL, stem cell source of peripheral or cord blood, and myeloablative regimen were identified as risk factors for stage-3 AKI until 100 days posttransplant. In a multivariable analysis, ferritin level >1000 ng/mL before HCT was the only independent risk factor for stage-3 AKI (adjusted HR 5.52; 95% CI, 2.21 to 13.76) (**Table 2**). Using backward stepwise selection, malignant disease and hyperferritinemia were identified as independent risk factors for stage-3 AKI (**Supplementary table 2**). When all of the relevant variables shown in **Table 1** were incorporated into the full model and then examined using backward stepwise selection, malignant disease and hyperferritinemia were the most significant independent factors for stage-3 AKI occurrence (**Supplementary table 3**).

Discussion

The most notable finding of the present study is that pretransplant hyperferritinemia in pediatric patients who undergo HCT is an important risk factor for stage-3 AKI after transplantation. The patients who developed stage-3 AKI in our study had lower survival rates within 100 days after HCT than those without stage-3 AKI. These results

suggest that pretransplant ferritin control is important for preventing severe AKI and subsequently improving the survival of pediatric patients.

In our study, the cumulative incidence of AKI was 80.7%, and that of stage-3 AKI was 50.7%, both of which were higher than in previous reports (21% to 53%) [3-7]. These reports mainly enrolled patients with lymphoid malignancy and aplastic anemia, whereas our study subjects had a high proportion of poorer prognostic diseases, such as myeloid leukemia, neuroblastoma, and hemophagocytic syndrome [4-7]. Pediatric patients with acute myeloid leukemia mainly receive myeloablative conditioning regimens based on busulfan or TBI [21], and those with aplastic anemia do not receive cancer chemotherapy prior to HCT [22]. Therefore, we speculated that myeloablative conditioning led to the increased cumulative incidence and severity of AKI in our subjects.

The risk factors for AKI after HCT, such as a high pre-HCT serum creatinine, non-HLA-identical related or a matched unrelated donor, VOD, cyclosporin, foscarnet, amphotericin B, and GVHD reported in pediatric patients have also been identified in adult patients [3,4, 6-8, 15]. However, hyperferritinemia has not been reported as a risk factor for AKI. Hyperferritinemia was shown to be strongly associated with reduced overall and disease-free survival rates in adult patients undergoing HCT [23, 24]. These findings promoted us to focus on the pre-transplant ferritin levels as a notable variable while investigating AKI factors. A preserved renal function is widely distributed in infants and children compared with adults. Considering the heterogeneity of the pediatric study population, the effect size of hyperferritinemia on the risk of severe AKI may be corroborated in the adult population. Further multicenter prospective studies are

needed to confirm the association between hyperferritinemia and renal damage in pediatric and adult patients undergoing HCT.

Hyperferritinemia represents not only iron overload but also inflammation with infection or pretreatment tissue injury. To eliminate the inflammatory effect, serum ferritin levels were assessed at the time of the pre-transplant phase free from infection. Moreover, serum ferritin levels more strongly correlated with the amount of blood transfused than the serum C-reactive protein levels (Spearman's rho 0.7481, $P<0.0001$; 0.3281. $P=0.0071$, respectively). It may raise a possibility that iron overload thus have a more severe effect than inflammation on kidney injury in pediatric patients with HCT.

Iron overload induces organ dysfunction, including heart failure, hypogonadism, renal tubular damage, glomerulonephritis and dyshemopoiesis [25-29]. Excessive iron, represented by hyperferritinemia, exerts cytotoxic effects by inducing the production of reactive oxygen species (ROS). ROS-activated signaling pathways mediate hematopoietic and non-hematopoietic cell death in patients who receive HCT [30]. Ferroptosis, which is an iron-dependent form of nonapoptotic cell death, has been recently considered as an explanation for most of the organ damage in cases of iron overload [31]. This mechanism of cell death also plays a pivotal role in inducing renal tubular damage after ischemic injury of the kidney [32]. Sheerin et al. [33] previously showed that the viability of proximal tubular epithelial cells was reduced by incubation with excessive iron *in vitro*. These reports support our hypothesis that iron overload may play an important role in the development of renal damage rerated HCT.

Hyperferritinemia is not only a predictor of AKI after HCT, but also provides a potential target for prevention. As mentioned above, hyperferritinemia represents iron overload as well as inflammation with infection or pretreatment tissue injury. It goes without saying that control of infection before transplantation is important. There is no effective treatment for chronic inflammation due to organ damage. Meanwhile, new control measures for iron overload are emerging. In terms of treatment, iron chelators like deferoxamine were reported to be effective for treating an experimental model of AKI in rats [34]. However, as conventional iron chelators induce nephrotoxicity, which can be exacerbated by calcineurin inhibitors, such as cyclosporin used for GVHD prophylaxis, iron chelators are not always recommended depending on the underlying diseases or concomitant medications [35]. Alternatively, hepcidin and neutrophil gelatinase-associated lipocalin, which regulate iron homeostasis, also attenuate kidney injury caused by ischemia [36, 37]. Iron control via the pathway of hepcidin and neutrophil gelatinase-associated lipocalin might thus be a promising therapeutic target for preventing AKI.

Stage-3 AKI patients had a high rate of relapse or graft failure compared with non-stage-3 patients (41% vs 20%, **Supplementary table 1**). On the contrary, stage-3 AKI patients had received second HCT less frequently than non-stage-3 patients (14% vs 86%, p=0.001). To date, there have been no reports that renal dysfunction affects relapse or graft failure. Because most patients with stage-3 AKI had malignant disease (85.3%), they were at risk of relapse. Furthermore, They had organ damage containing renal failure or the deteriorated performance status. This speculation reflected by that both two re-transplanted patients with stage-3 AKI suffered from malignant diseases

and 3 of 6 re-transplanted patients without stage-3 AKI suffered from non-malignant diseases.

There are several limitations associated with our study. It was a single-center study that included a small cohort of patients. VOD/SOS was not analyzed as a variable because of its rarity in our institution, although it was reported to be a risk factor for AKI following HCT. Furthermore, our analysis does not include all infants and children, as the standard Japanese GFR estimation formula cannot be applied to infants under 2 years old.

In conclusion, we found that hyperferritinemia increased the risk of stage-3 AKI after HCT in pediatric patients. There was a close associate between serum ferritin levels and total amount of blood transfused. Pretransplant iron control may reduce the development of severe AKI and improve the patient survival rate. Further studies are needed to confirm the results and prepare appropriate interventions for pediatric patients receiving HCT.

Conflict of Interest statement

The authors have no conflicts of interest to declare.

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Figure legends

Figure 1. Flowchart of the selection of 69 pediatric patients who received allogenic HCT. Among the 115 patients who received hematopoietic cell transplantation (HCT) in our institution, we excluded the 39 patients who were unsuited to having their estimated glomerular filtration rate (eGFR) calculated using the formula for Japanese children and adolescents, as well as the 7 patients who had a low eGFR before HCT. AKI: acute kidney injury.

Figure 2. Kaplan-Meier curves showing the overall survival (OS) among those with (solid line) and without (dotted line) stage-3 AKI during the early period (0-100 days) (A) and the late period (101-365 days) (B).

Supplementary figure. The number of deaths and causes of death at 2 time points (100 days and 365 days after HCT) in the study population. Closed circles indicate the patients with stage-3 AKI within 100 days after HCT, and open circles indicate the patients without stage-3 AKI within 100 days after HCT. The 10 deceased patients were classified by their cause of death: treatment-related events, relapse or graft failure, and events after second HCT.

Figure 1

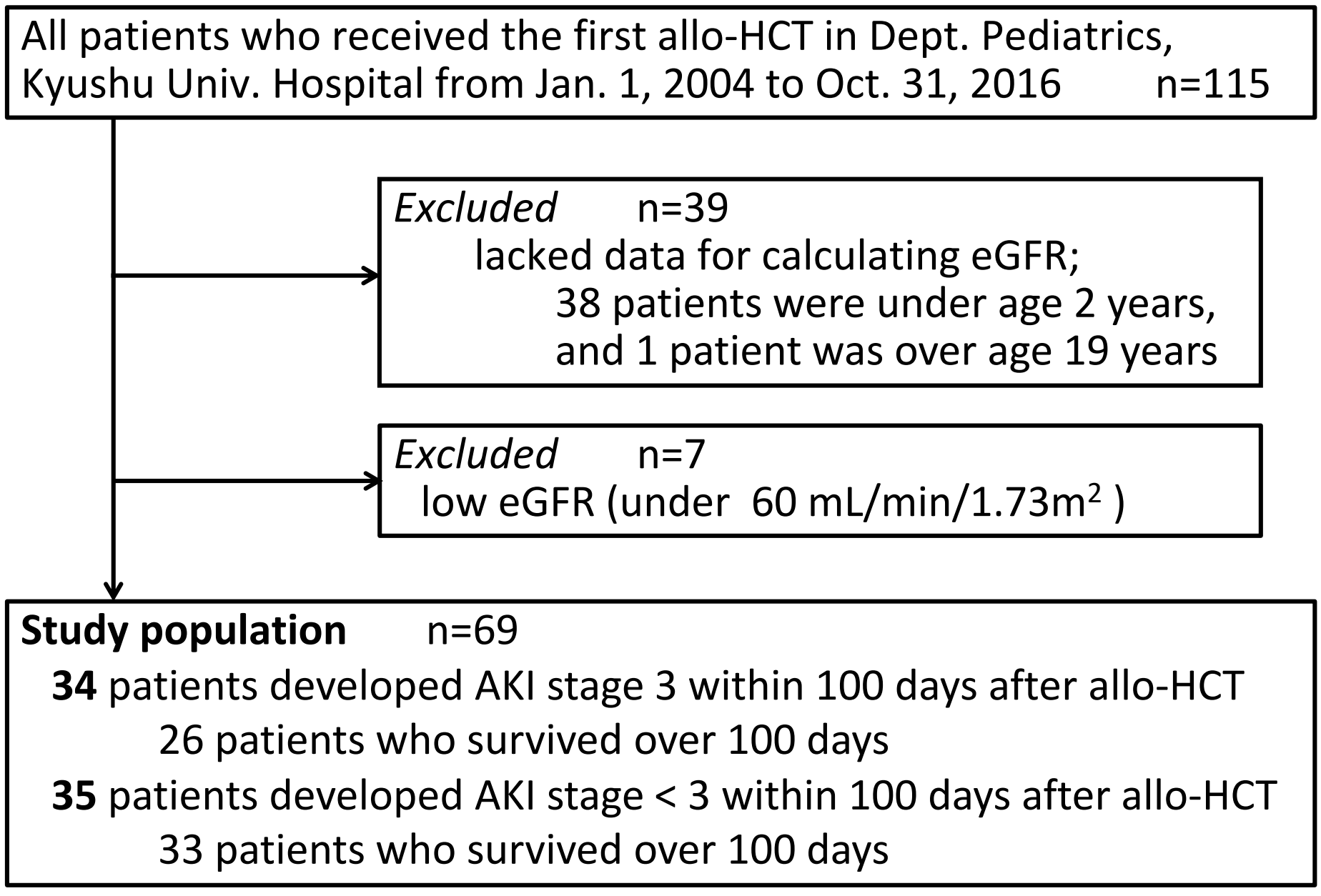
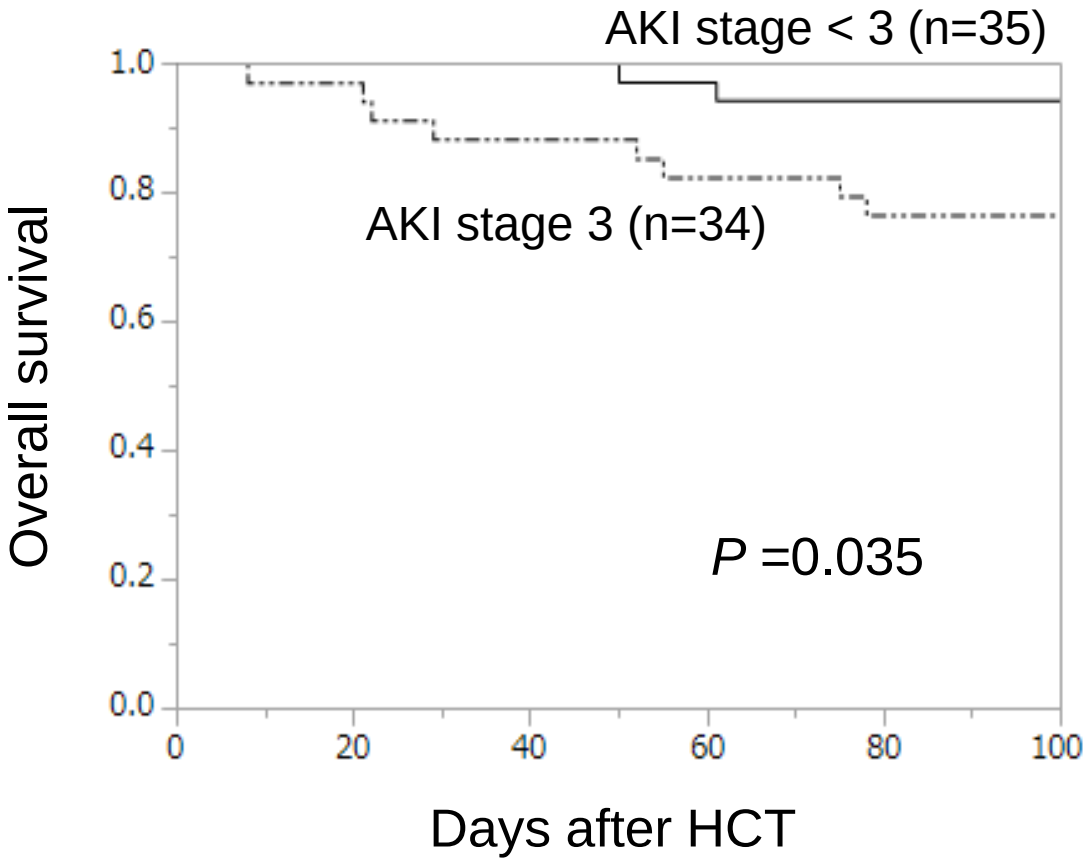
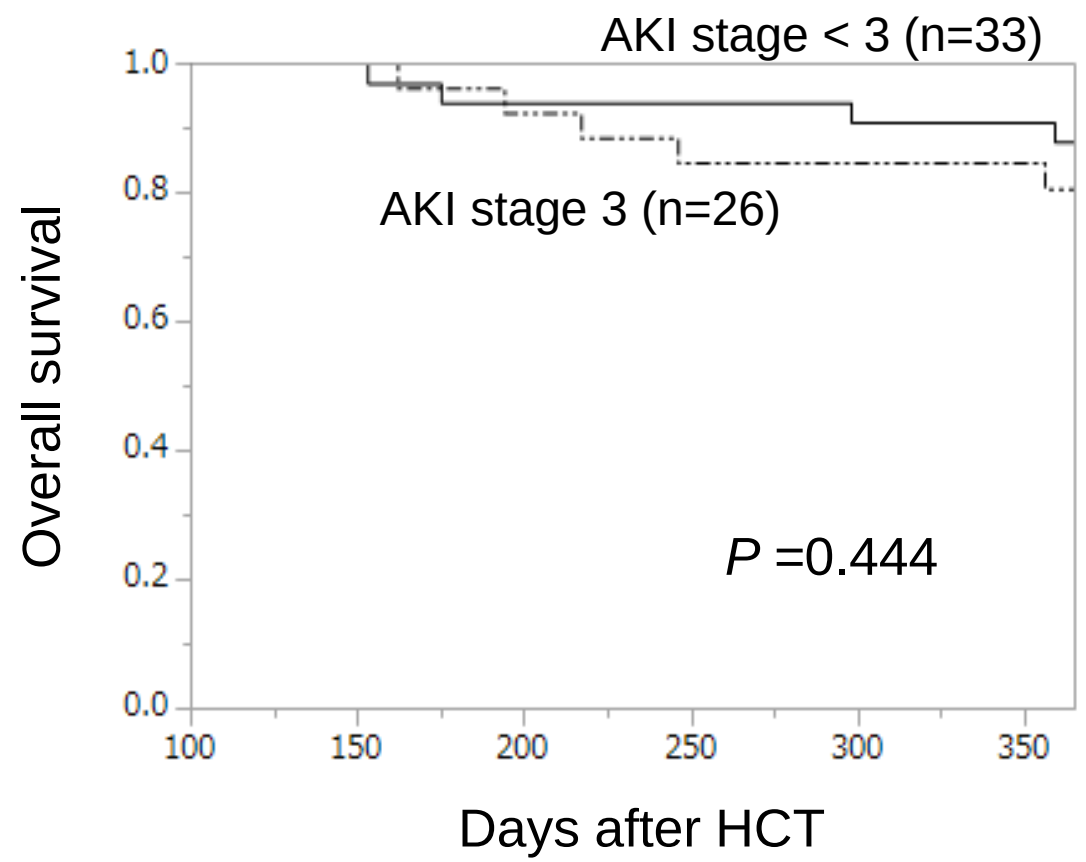
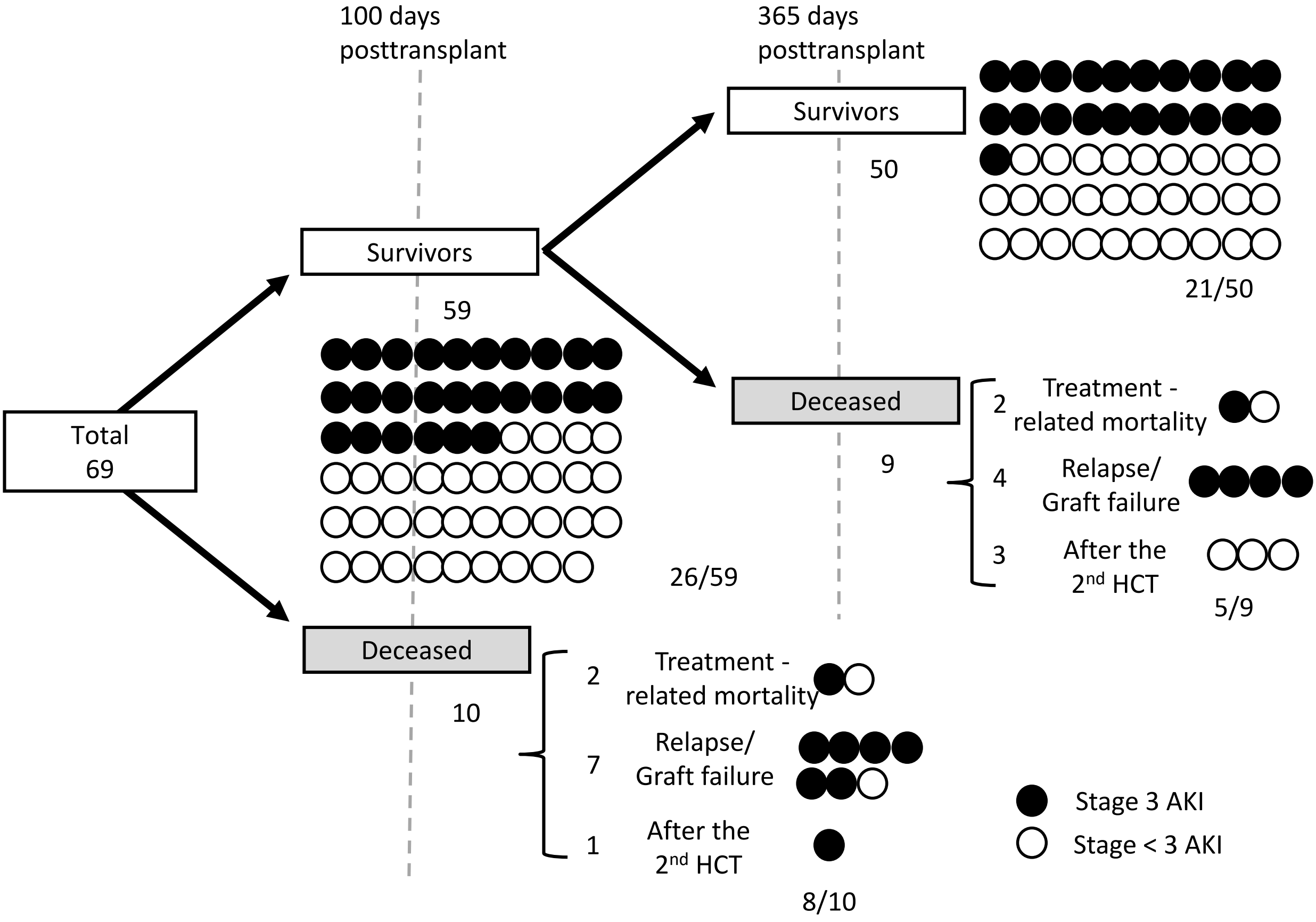

All patients who received the first allo-HCT in Dept. Pediatrics, Kyushu Univ. Hospital from Jan. 1, 2004 to Oct. 31, 2016 n=115
Excluded n=39
lacked data for calculating eGFR;
38 patients were under age 2 years,
and 1 patient was over age 19 years
Excluded n=7
low eGFR (under 60 mL/min/1.73m2)
Study population n=69
34 patients developed AKI stage 3 within 100 days after allo-HCT
26 patients who survived over 100 days
35 patients developed AKI stage < 3 within 100 days after allo-HCT
33 patients who survived over 100 days

Figure 2

A


AKI stage < 3 (n=35)
AKI stage 3 (n=34)
P =0.035
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
Days after HCT

B


AKI stage < 3 (n=33)
AKI stage 3 (n=26)
P =0.444
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
100
150
200
250
300
350
Days after HCT

Supplementary figure