Incidence of acute kidney disease after receiving hematopoietic stem cell transplantation: a single-center retrospective study

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ABSTRACT

Background. Previous reports have shown that acute kidney injury (AKI) is common after hematopoietic stem cell transplantation (HSCT), which is a crucial treatment for patients with hematological disorders. AKI could increase mortality and induce adverse effects including the development of chronic kidney disease. The incidence of AKI in association with HSCT reportedly varies significantly because several definitions of AKI have been adopted. Acute kidney disease (AKD) is a new concept that can clinically define both AKI and persistent decreases in glomerular filtration rate (GFR) state. We conducted a retrospective cohort study to determine the incidence of AKD after HSCT.

Methods. This study included 108 patients aged between 16 and 70 years undergoing HSCT. In this study, AKD included clinical condition of AKI or subacute decreases in GFR. AKI was defined according to the Kidney Disease: Improving Global Outcomes guidelines based on serum creatinine. However, urine output data were not included to define AKI because the

30   database lacked some of these data. Comparisons were made between groups using the Mann-

31   Whitney U test.

32   **Results.** AKD occurred in 17 patients (15.7%). There were significant differences between the

33   AKD and non-AKD with respect to ABO-incompatible HSCT (p=0.001) and incidence of acute

34   graft versus host disease (GVHD) after HSCT (p<0.001). The 100-day overall survival of

35   patients with AKD and without AKD after HSCT was 70.6% and 79.8%, respectively (p=0.409).

36   **Discussion.** ABO-incompatible HSCT and acute GVHD after HSCT were risk factors for the

37   incidence of AKD. However, we could not find a significant association between AKD after

38   HSCT and mortality.

39

40   **INTRODUCTION**

41   Hematopoietic stem cell transplantation (HSCT) is a fundamental therapy for high risk

42   and refractory hematological diseases. Several types of HSCT procedures exist based on

43   conditioning therapy (myeloablative or reduced intensity), donor source (autologous and

44   allogenic, including matched related, matched unrelated, haploidentical and umbilical cord) and

45   stem cell source (peripheral blood stem cells or bone marrow stem cells) [1, 2]. Acute kidney

46   disease (AKD) can lead to chronic kidney disease (CKD) with increased all-cause mortality.

47   Although acute kidney injury (AKI) is a well-defined concept, AKD definition is relatively new

48   [3]. To diagnose AKI more accurately, the new concept of AKI definition has been proposed by

49   the Kidney Disease Improving Global Outcomes (KDIGO), which is based on and modified by

50   the risk, injury, failure, loss of function, end-stage renal disease (RIFLE) classification and the

51   Acute Kidney Injury Network (AKIN) criteria [3-6]. AKD is defined as subacute reduction in

52   glomerular filtration rate (GFR), including AKI clinical states [7, 8].

53   Previous reports have shown that AKI is relatively common after HSCT, and it could

54   increase mortality and induce adverse effects including the development of CKD [9]. Previous

55   reports indicated that the incidence of AKI in association with HSCT ranged from 20% to 73%

56   [10], while other studies indicated 42% to 92% [11] . Study results based on these data have been

57   varied because several definitions of AKI have been adopted.

58   Acute graft versus host disease (GVHD) occurs within the first 3 months after HSCT

59   and involves the reactivity of donor immune cells against host tissues [12]. Therefore, when

60   evaluating kidney damage in acute GVHD, the conventional definition of AKI, in which AKI

61 should be diagnosed within 1 week, may not be suitable. Thus, we used the definition of AKD,

62 which is a new concept and could clinically define both AKI and persistent decreases in GFR

63 state. We conducted a retrospective cohort study to determine the incidence of AKD after HSCT.

64

65 **MATERIALS & METHODS**

66

67 **Patient groups**

68   All procedures performed in studies involving human participants were in accordance

69 with the ethical standards of the institutional and/or national research committee and with the

70 1964 Helsinki declaration and its later amendments or comparable ethical standards. This is a

71 retrospective medical record review study. The retrospective waiver of consent was obtained

72 from the clinical study ethics review board of Kindai University Nara Hospital (approval

73 number: 18-6).

74   This study included a retrospective cohort of 108 patients who underwent HSCT at

75 Kindai University Nara Hospital from May 2006 to April 2016. Data were collected and

76 analyzed retrospectively using electronic medical records maintained by the Department of

77 Nephrology and Hematology at Kindai University Nara Hospital. Data including year of HSCT,

78 HSCT characteristics (e.g., underlying disease, donor type, total body irradiation, ABO

79 incompatibility, and calcineurin inhibitor-based GVHD prophylaxis), indications for HSCT,

80 acute GVHD, AKD, and survival outcomes were obtained from the electronic medical records

81 and transplant database.

82

83 **Definition of AKD**

84   AKD was defined to include clinical condition of AKI or subacute decreases in GFR

85 (i.e., GFR<60 ml/min/1.73 m^2 for less than 3 months or decrease in GFR by ≥35% or increase in

86 serum creatinine by >50% for less than 3 months) [7, 8]. AKI was defined according to KDIGO

87 guidelines based on serum creatinine [3]. However, urine output data were not included in our

88 definition of AKI because some data were not available in the database.

89

90 **Statistical analysis**

91   Continuous variables were presented as medians with interquartile ranges (IQRs).

92   Comparisons were made between groups using the Mann-Whitney U test; categorical variables

93   were presented as numbers (percentage) and compared using the Fisher's exact tests. According

94   to clinical features and previous reports which indicated the association with AKD after HSCT,

95   12 variables (age, sex, height, weight, underlying disease, with or without hypertension, with or

96   without diabetes mellitus, total body irradiation, ABO compatibility, acute GVHD, calcineurin

97   inhibitor-based GVHD prophylaxis, and donor and cell source) were eligible for this study.

98   The 100-day overall survival of patients with or without AKD after HSCT was

99   estimated using the Kaplan-Meier method and compared using the log-rank test. All analysis was

100   performed using StatView (SAS Institute, Cary, CA, USA). Statistical significance was defined

101   as $p<0.05$.

102

103   **RESULTS**

104   We determined the clinical characteristics of 108 patients who underwent HSCT. The

105   median age of the study participants was 49 (IQRs; 16-70) years, and 39 (36.1%) were women.

106   The median height was 166 (IQRs; 149-184) cm and body weight was 58 (IQRs; 35-95) kg.

107   Underlying diseases were as follows: acute lymphoblastic leukemia (ALL: 15 cases, 13.9%),

108   acute myeloblastic leukemia (AML: 43 cases, 39.8%), chronic myeloblastic leukemia (CML: 4

109   cases, 3.7%), myelodysplastic syndromes (MDS: 10 cases, 9.3%), multiple myeloma (MM: 5

110   cases, 4.6%), aplastic anemia (AA: 6 cases, 5.6%), and others (25 cases, 23.1%). Hypertension

111   and diabetes were observed in 12 (11.1%) and 9 cases (8.3%), respectively. Body irradiation

112   more than 8 Gy was observed in 79 cases (73.1%). ABO-incompatible HSCT was performed in

113   18 cases (16.7%). Acute GVHD after HSCT occurred in 17 cases (15.7%) and calcineurin-based

114   GVHD prophylaxis was given in 67 cases (62.0%). Donor and cell sources were as follows:

115   allogenic bone marrow transplantation (Allo-BMT: 20 cases, 18.5%), unrelated umbilical cord

116   blood transplantation (UR-CBT: 38 cases, 35.2%), unrelated bone marrow transplantation (UR-

117   BT: 26 cases, 24.1%), allogenic peripheral blood stem cell transplantation (Allo-PBSCT: 11

118   cases, 10.2%), and autologous peripheral blood stem cell transplantation (Auto-PBSCT: 16 cases,

119   14.8%). AKD developed in 17 cases (15.7%) within 100 days of HSCT. Furthermore, four out of

120   17 AKD cases required hemodialysis. We assessed the association of AKD with the clinical

121   characteristics as mentioned above. There were significant differences between the AKD and

122   non-AKD with respect to ABO-incompatible HSCT (p=0.001) and incidence of acute GVHD

123 after HSCT (p<0.001). However, we could not find a significant association between AKD and

124 other clinical characteristics (Table 1). Then, we analyzed the 100-day overall survival of

125 patients with AKD and without AKD after HSCT. The overall survival rate was 70.6% and

126 79.8%, respectively (p=0.409). Thus, we could not find a significant association between HSCT-

127 induced AKD and mortality (Figure 1).

128

129 **DISCUSSION**

130   This retrospective, single-center study focused on the incidence of AKD after HSCT.

131 Our results could offer the probability of searching the risk and prognostic factor of AKD after

132 HSCT and provide a deeper understanding of this disorder. We found that the incidence of AKD

133 after HSCT was 15.7%. Furthermore, ABO-incompatible HSCT and the incidence of acute

134 GVHD were independently associated with AKD. However, we could not find a significant

135 association between AKD and mortality after HSCT.

136   Previous reports indicated that the incidence of AKI among HSCT recipients varies

137 widely from 20% to 92% [10, 11]. This difference has varied significantly because of the

138 variations in AKI definitions. Especially, most previous studies defined AKI using simply the

139 doubling of serum creatinine, and this could exclude early-stage AKI. KDIGO proposed a new

140 AKI definition which has been integrated from AKIN and RIFLE [3]. However, despite using

141 the KDIGO definition, acute GVHD-related kidney injury could not be evaluated properly,

142 because most acute GVHDs occur within 100 days after HSCT. There were no accurate urinary

143 volume data in our study, but when evaluating AKI according to serum creatinine level alone,

144 only two cases (stages 1 and 3) could be diagnosed as AKI. These results also support that the

145 conventional AKI definition could not be suitable for acute GVHD-related renal injury.

146   Incidence of AKD in our study was lower than previous reports. Several reasons could

147 be considered. First, medications that can decrease glomerular perfusion, such as renin

148 angiotensin system inhibitors (RASI) or NSAIDs were used in our study very few; RASI were

149 used in 2 cases (1.9%) and NSAIDs were used in 4 cases (3.7%), respectively. Second, diabetes

150 which could exacerbate renal function was recognized only 9 cases (8.3%) in our study. Third, as

151 previously indicated, early involvement of the nephrologist in our case might prevent incidence

152 of AKD [10, 13].

153   Induction of combination therapy cyclosporine or tacrolimus, calcineurin inhibitors

154 (CNIs) and methotrexate could be superior to calcineurin inhibitors alone in the prophylaxis of

155 acute GVHD. Although there was no correlation between the incidence of AKD and the use of

156 calcineurin inhibitors (CNIs) in our study, several mechanisms by which cyclosporine use leads

157 to renal injury are proposed. Previous reports indicated that CNIs induced glomerular endothelial

158 dysfunction and renal artery smooth muscle cell contraction, leading to AKD [13, 14]. Our study

159 showed no correlation between CNIs and incidence of AKD. Much of the renal toxicity of CNIs

160 is thought to be dose dependent. One possibility is that CNIs levels in the blood were monitored

161 strictly to prevent side effects in our study. CNIs could activate renin angiotensin II system

162 (RAS), which increases phospho-c-Raf (Ser338) and Erk1/2 phosphorylation increasing

163 extracellular matrix [15]. RAS also causes vasoconstriction of renal arterioles, inducing AKI [14,

164 16, 17].

165 The association between AKI and the incidence of GVHD has been reported. After

166 HSCT, kidneys are exposed to GVHD-induced systemic inflammation. Donor T-cells and

167 endothelial dysfunction are also key aspects of developing AKI in GVHD [13]. Further,

168 increases in several cytokines could trigger kidney injury in acute GVHD; when acute GVHD

169 occurred, interleukin (IL)-2, IL-6, or tumor necrosis factor-α was upregulated in the kidney [18-

170 20]. These cytokines are produced during the initial step of GVHD, resulting in AKD.

171 Furthermore, prolonged increases in these inflammatory cytokines could lead to CKD [15, 21].

172 Another important mechanism of developing GVHD is invasion of inflammatory cells, such as

173 macrophages and monocyte in various organs. Previously, mononuclear cell or T-cell infiltration

174 of renal vessels was reported to be associated with GVHD [19, 22]. GVHD or cytokines released

175 from GVHD could induce endothelial dysfunction, resulting in thrombotic microangiopathy

176 (TMA). TMA includes thrombocytopenic purpura and hemolytic uremic syndrome. Generally,

177 HSCT-induced TMA is not related to deficiencies in von Willebrand factor-cleaving protease,

178 but to endothelial dysfunction from GVHD-induced direct cell injury or by several cytokines

179 derived from GVHD occurring in other parts of the body.

180 The relationship between ABO-incompatible HSCT and AKD is still unclear. However,

181 ABO incompatibility could induce GVHD; ABO antigens are recognized in several organs

182 including endothelial cells where donor origin blood cells might attack, triggering GVHD [23,

183 24]. Thus, there is a possibility that ABO incompatibility-induced GVHD is a major risk of AKD

184 in our study rather than ABO incompatibility and GVHD respectively.

185   Hepatic sinusoidal obstruction syndrome (SOS), previously known as veno-occlusive

186   disease, is one of the major complications after HSCT and could be an independent risk factor

187   for AKD development. The mechanisms of SOS-induced AKD are still unclear, but one

188   possibility is that SOS may exacerbate liver function itself, resulting in hepatorenal syndrome.

189   Moreover, some reports have suggested that endothelial dysfunction is essential for SOS

190   development. We have shown that plasminogen activator inhibitor (PAI)-1 was increased in

191   endothelial dysfunction [15]. Furthermore, previous reports indicated that the levels of PAI-1

192   expression could be diagnostic and predicting marker for SOS [25, 26]. In addition, use of

193   TBI>12 Gy could be one of the risk factors for SOS [27]. In the present study, nine patients

194   underwent total body irradiation with more than 12 Gy, but development of SOS was not

195   recognized in any patients.

196   Despite the absence of data on endothelial function, such as PAI-1, von Willebrand

197   factor, or a disintegrin-like metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS

198   13) in our study, endothelial dysfunction might be induced by HSCTs among the AKD patients.

199   Previous reports indicated that ABO-incompatible HSCT increased the incidence of SOS,

200   leading to AKD [28, 29]. Our data indicated that ABO-incompatible or GVHD-related AKD did

201   not affect the overall survival. Similar to our results, several previous reports showed an

202   increased mortality in ABO-incompatible transplants without an effect on overall survival [28,

203   29], while Kimura et al. showed lower overall survival and increased mortality rates in ABO-

204   mismatched transplants [30]. Thus, it is still unclear whether ABO-incompatible HSCT increases

205   AKD and mortality rates.

206   There might be some limitations to our study, because this was a retrospective analysis

207   and a single-center study. Several reasons could be considered. First, we could not adequately

208   examine urine volume associated with diagnosis of AKI and we used serum creatinine as the

209   principal criterion in the definition of AKD. Second, we did not have data on cytomegalovirus

210   infection that often recognized in HSCT and can increase inflammation in kidney. Third, we did

211   not have precise data on severity of acute GVHD. Lastly, we did not have renal pathological data

212   that could help to enhance the understanding etiology of AKD. We would like to improve study

213   protocol including periodic urinalysis and renal biopsies.

214

215

216 **CONCLUSIONS**

217   There is an association with ABO-incompatible HSCT and AKD as well as an

218 association with HSCT related acute GVHD and AKD. GVHD and ABO-incompatible HSCT

219 emerges important cause of AKD regardless nephrotoxic agents. Our data also demonstrated that

220 mortality was not increased with the incidence of AKD.

221

222 **ACKNOWLEDGMENTS**

223   Part of this manuscript was presented at the 2nd Asia Pacific AKI CRRT Congress

224 2018. We wish to thank Hitoshi Hanamoto, Hideo Yagi, and Mariko Fujita for consultation on

225 the work-up of the patients and this study.

226

227 **FIGURE LEGEND**

228 **Figure 1. Overall survival by acute kidney disease after hematopoietic stem cell**

229 **transplantation.**

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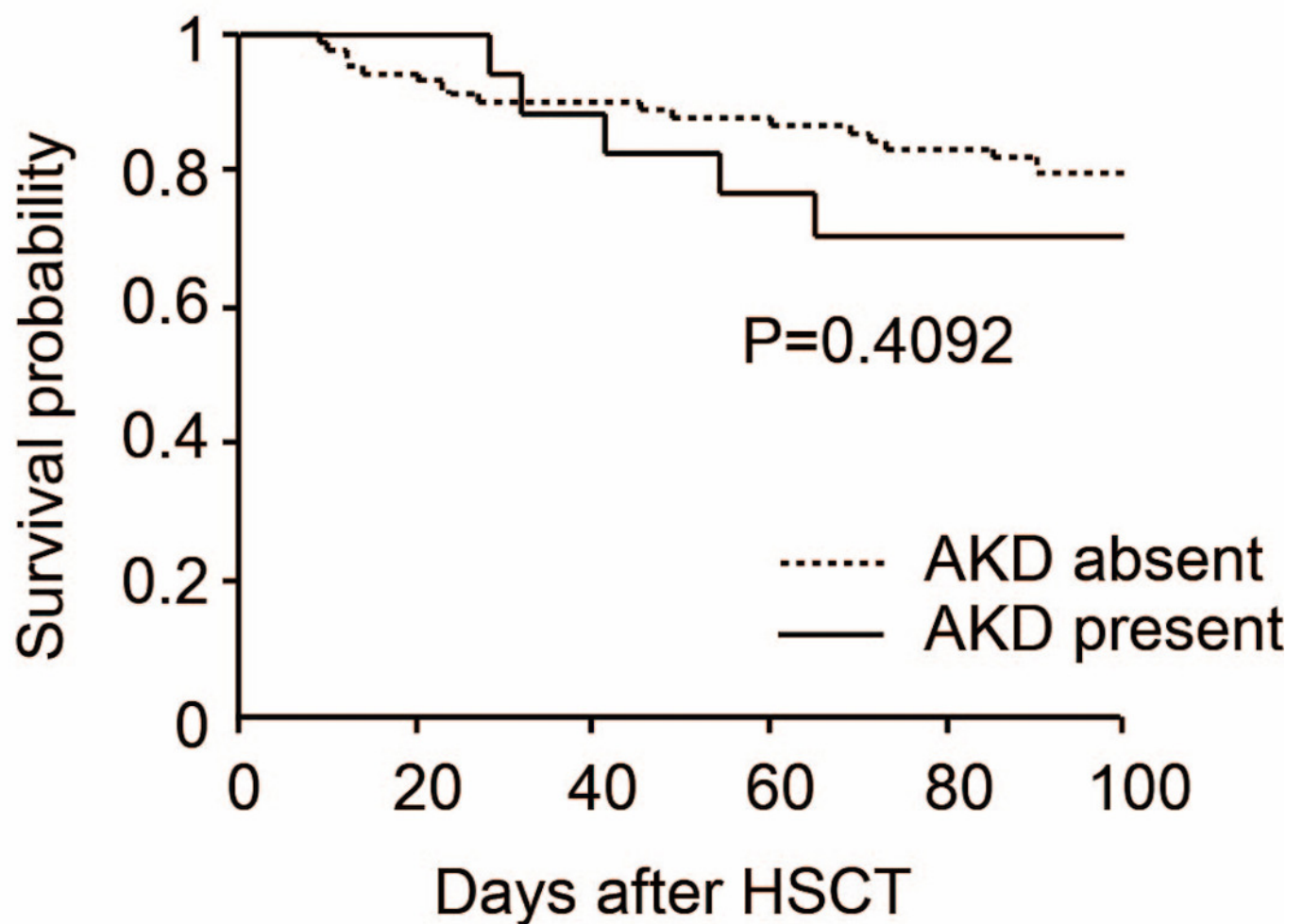
338

339

Figure 1

Overall survival by acute kidney disease after hematopoietic stem cell transplantation.

Univariable association between patient characteristics and post-hematopoietic stem cell transplantation.

1 **Table1. Univariable association between patient characteristics and post-hematopoietic stem cell transplantation**

Variables	All patients (n=108)	Acute kidney disease		P value
		Absent (n=91)	Present (n=17)	
Age (years)	49 (16-70)	49 (17-70)	49 (16-66)	0.574
Female gender	39 (36.1%)	34(31.5%)	5(4.6%)	0.594
Height (cm)	166 (149-184)	166 (150-184)	168 (149-176)	0.823
Weight (kg)	58 (35-95)	59 (35-95)	53.5 (43-77)	0.232
Underlying disease				
ALL	15 (13.9%)	13 (12.0%)	2 (1.9%)	0.288
AML	43 (39.8%)	37 (34.2%)	6(5.6%)	0.592
CML	4 (3.7%)	4 (3.7%)	0 (0%)	0.999
MDS	10 (9.3%)	7 (6.5%)	3 (2.8%)	0.371
MM	5 (4.6%)	5 (4.6%)	0 (0%)	0.999
AA	6 (5.6%)	4 (3.7%)	2 (1.9%)	0.265
Others	25 (23.1%)	24 (22.2%)	1 (0.9%)	0.063
HTN	12 (11.1%)	2 (1.9%)	10 (9.3%)	0.999
DM	9 (8.3%)	7 (6.5%)	2 (1.9%)	0.628
TBI ≥ 8Gy	79 (73.1%)	67 (62.0%)	12 (11.1%)	0.726
ABO incompatible	18 (16.7%)	10 (9.3%)	8 (7.4%)	0.001
Acute GVHD	17 (15.7%)	7 (6.5%)	10 (9.3%)	<0.001
CNI-based GVHD prophylaxis	67 (62.0%)	56 (51.2%)	11 (0.2%)	0.999
Donor and cell source				
Allo-BMT	20 (18.5%)	17 (15.7%)	3 (2.8%)	0.999
UR-CBT	38 (35.2%)	31 (28.7%)	7 (6.5%)	0.589

UR-BMT	26 (24.1%)	21 (19.4%)	5 (4.6%)	0.550
Allo-PBSCT	11 (10.2%)	10 (9.3%)	1 (0.9%)	0.999
Auto-PBSCT	16 (14.8%)	15 (13.9%)	1 (0.9%)	0.458

2 ALL: acute lymphoblastic leukemia, AML: acute myeloblastic leukemia, CML: chronic myeloblastic leukemia, MDS:

3 myelodysplastic syndromes, MM: multiple myeloma, AA: aplastic anemia, HTN: hypertension, DM: diabetes mellitus, TBI: total

4 body irradiation, GVHD: graft versus host disease, CNI: calcineurin inhibitor, Allo: allogenic, BMT: bone marrow transplantation,

5 UR: unrelated, CBT: umbilical cord blood transplantation,

6 PBSCT: peripheral blood stem cell transplantation, Auto: autologous