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Prognostic factors of pediatric hematopoietic stem cell transplantation recipients admitted to the pediatric intensive care unit

Da Hyun Kim, Eun Ju Ha, Seong Jong Park, Kyung-Nam Koh, Hyery Kim, Ho Joon Im, Won Kyoung Jhang

Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Korea

Background: Pediatric patients who received hematopoietic stem cell transplantation (HSCT) tend to have high morbidity and mortality. While, the prognostic factors of adult patients received bone marrow transplantation were already known, there is little known in pediatric pateints. This study aimed to identify the prognostic factor for pediatric intensive care unit (PICU) mortality of critically ill pediatric patients with HSCT.

Methods: Retrospectively reviewed that the medical records of patients who received HSCT and admitted to PICU between January 2010 and December 2019. Mortality was defined a patient who expired within 28 days.

Results: A total of 131 patients were included. There were 63 boys (48.1%) and median age was 11 years (interquartile range, 4–15 years). The most common HSCT type was haploidentical (38.9%) and respiratory failure (44.3%) was the most common reason for PICU admission. Twenty-eight-day mortality was 22.1% (29/131). In comparison between survivors and non-survivors, the number of HSCTs received, sepsis, oncological pediatric risk of mortality-III (OPRISM-III), pediatric risk of mortality-III (PRISM-III), pediatric Sequential Organ Failure Assessment (pSOFA), serum lactate, B-type natriuretic peptide (BNP) and use of mechanical ventilator (MV) and vasoactive inotropics were significant predictors ($P<0.05$ for all variables). In multivariate logistic regression, the number of HSCTs received, use of MV, OPRISM-III, PRISM-III and pSOFA were independent risk factors of PICU mortality. Moreover, three scoring systems were significant prognostic factors of 28-day mortality.

Conclusions: The number of HSCTs received and use of MV were more accurate predictors in pediatric patients received HSCT.

Key Words: hematopoietic stem cell transplantation; mortality; pediatric intensive care unit; prognosis

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Corresponding author
Won Kyoung Jhang
Division of Pediatric Critical Care Medicine, Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-5936
Fax: +82-2-3010-6978
E-mail: wkjhang@amc.seoul.kr

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is currently used as a treatment for high-risk or relapsed hematologic malignancies and non-malignant hematologic disease [1,2]. For successful transplantation, recipients have to overcome several complications such as sepsis, graft versus host disease (GVHD), thrombotic microangiopathies, and veno-occlusive

disease that occur after HSCT [3-5]. To prevent complications, the HSCT protocol has been reorganized across areas such as precise human leukocyte antigen (HLA) typing, graft manipulation, conditioning regimen, prophylactic antibiotics, or antifungal agents [5-8]. Also, intensive care management has been improved with time [9]. However, a significant proportion of adult and pediatric recipients still become critically ill, requiring admission to the intensive care unit (ICU). Many factors, including preexisting disease, transplant-related toxicity, infection, and sequelae of pre- or post-transplant organ damage, are thought to be contributory.

As the number of HSCTs patients increases, the number of patients admitted to the ICU also increases. Thus, many investigators are working on identifying the prognostic factors of ICU mortality. Several HSCT-related factors, such as underlying disease, type of HLA mismatch, failure of neutrophil engraftment, presence of GVHD, and cytomegalovirus (CMV) seropositivity are associated with increased mortality after HSCT [10-12]. Critical care interventions, such as mechanical ventilator (MV), renal replacement therapy, vasoactive inotropes were known to be the significant factors of mortality [13]. Moreover, many studies have assessed the correlation between scoring systems, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS), and Sequential Organ Failure Assessment (SOFA) scores, and mortality in adults [11,14]. However, for pediatric patients, only a few such studies have assessed the severity of illness in HSCT patients as a prognostic factor, and there are only a few studies on the reappraisal of pediatric HSCT recipients. Pedaitric HSCT patients have increased severity in a variety of forms when they admit pediatric intensive care unit (PICU) and the prognostic factors resulting from mortality have been also rarely studied. Thus, we reviewed that the critical ill pediatric patients admitted to the ICU to identify the significant risk factors, especially severity illness of scores, which can predict mortality.

KEY MESSAGES

- Pediatric patients who received hematopoietic stem cell transplantation (HSCT) tend to have several complications and have high mortality.
- The number of HSCTs received, use of mechanical ventilator, oncological pediatric risk of mortality-III (OPRISM-III), pediatric risk of mortality-III (PRISM-III), and pediatric Sequential Organ Failure Assessment (pSOFA) were significant prognostic factor of 28-day mortality.

MATERIALS AND METHODS

Patients

We investigated all HSCT recipients admitted to the 14-bed multidisciplinary PICU of Asan Medical Center Children's Hospital, Seoul, Korea between January 2010 and December 2019. We excluded patients who had insufficient data necessary for severity scoring and patients with a Do-Not-Resuscitate order in place. The Institutional Review Board of the Asan Medical Center approved this study (IRB No. 2020-0382) and parental consent was waived due to the retrospective nature of the analyses.

Data Collection

We retrospectively reviewed the electrical medical records of the enrolled patients and obtained data, including age at PICU admission, sex, underlying hemato-oncologic disease, length of PICU stay, and mortality. The HSCT parameters, including HSCT type, development of acute GVHD, CMV infection, veno-occlusive disease, and transplant-associated thrombotic microangiopathy were evaluated. The clinical and biological variables, including vital signs, arterial blood gas analysis, and laboratory results, such as complete blood count, chemistry profiles, coagulation profiles, and C-reactive protein, serum lactic acid, and B-type natriuretic peptide (BNP) levels were analyzed. For identifying the severity of disease, we used the oncological pediatric risk of mortality-III (OPRISM-III), pediatric risk of mortality-III (PRISM-III), and pediatric Sequential Organ Failure Assessment (pSOFA) scores calculated within 24 hours of PICU admission. The PRISM-III consists of cardiovascular/neurologic vital signs, acid-base/blood gas values, and chemical (glucose, creatinine, potassium, and blood urea nitrogen), and hematologic laboratory values (white blood cell count, platelet count, and coagulation profile) [15]. The pSOFA comprises the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) ratio, platelet count, bilirubin level, mean arterial pressure (MAP) or vasoactive infusion, Glasgow coma scale (GCS) score, and creatinine level [16]. The PRISM-III and pSOFA were often used to evaluate multiorgan failure in critically-ill pediatric patients, and the OPRISM-III, a modification of the PRISM-III, was used for assessing children after HSCT [17]. During ICU management, the need for invasive MV, continuous renal replacement therapy, and vasoactive inotropic drugs were monitored. Mortality was

defined as a patient who died within 28 days during the PICU stay. The primary outcome was the PICU 28-days mortality and the secondary outcome was risk factors that predisposed to mortality.

Statistical Analysis

All data were analyzed using the IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as median with interquartile range or mean±standard deviation and a two-tailed Student t-test, as appropriate. We used the chi-square or two-tailed Fisher's exact tests to analyze categorical variables. We used the multivariate logistic regression analysis to interrogate variables to find independent risk factors. We calculated the area under the curve (AUC) and the

Table 1. Baseline characteristics of the study population

Variable	Total (n=131)	Survivor (n=102)	Non-survivor (n=29)	P-value
Male	63 (48.1)	50 (49)	13 (44.8)	0.690
Age at HSCT	9.46 (3.14–14.79)	9.54 (2.63–14.84)	9.46 (3.26–15.42)	0.939
Age at PICU admission	11.00 (4.00–15.00)	11.00 (4.00–25.00)	9.00 (3.00–15.00)	0.233
Length of PICU stay (day)	16.94±27.43	19.54±30.34	7.79±7.87	0.041
Underlying hemato-oncologic disease				0.731
Leukemia	67 (51.1)	53 (52)	14 (48.3)	
Lymphoma	7 (5.3)	6 (5.9)	1 (3.4)	
Non-malignant hematologic disease	26 (19.8)	21 (20.6)	5 (17.2)	
Solid tumor	31 (23.7)	22 (21.6)	9 (31)	
Types of donor				0.160
HLA matched (related)	9 (6.9)	9 (8.8)	2 (6.9)	
HLA matched (unrelated)	37 (28)	31 (30.4)	4 (13.8)	
HLA mismatched (related)	53 (40.4)	35 (34.3)	16 (55.2)	
HLA mismatched (unrelated)	5 (3.8)	5 (4.9)	0	
Autologous	27 (20.6)	20 (19.6)	7 (24.1)	
No. of HSCTs				0.013
1	106 (80.9)	88 (86.3)	18 (62.1)	
≥2	25 (19.1)	14 (13.7)	11 (37.9)	
Day from HSCT to admission				0.064
<30	21 (16.0)	14 (13.7)	7 (24.1)	
31–99	23 (17.6)	15 (14.7)	8 (27.6)	
>100	87 (66.4)	73 (71.6)	14 (48.3)	
Main reason for PICU admission				0.460
Respiratory failure	58 (44.3)	45 (44.1)	13 (44.8)	
Neurologic defect	18 (13.7)	12 (11.8)	6 (20.7)	
Sepsis	17 (13.0)	13 (12.7)	4 (13.8)	
Renal failure	12 (9.2)	10 (9.8)	2 (6.9)	
Hemato-oncology complication	12 (9.2)	10 (9.8)	2 (6.9)	
Cardiovascular disease	7 (5.3)	7 (6.9)	0	
Gastro-intestinal disease	7 (5.3)	5 (4.9)	2 (6.9)	
CMV infection	35 (26.7)	29 (28.4)	6 (20.7)	0.406
Veno-occlusive disease	9 (6.9)	7 (6.9)	2 (6.9)	0.995
Graft-versus-host disease	28 (21)	18 (17.6)	10 (34.5)	0.135
TA-TMA	13 (9.9)	11 (10.8)	2 (6.9)	0.537
Septic shock	17 (13.0)	13 (12.7)	4 (13.8)	0.022

Values are presented as number (%), median (interquartile range), or mean±standard deviation.
HSCT: hematopoietic stem cell transplantation; PICU: pediatric intensive care unit; HLA: human leukocyte antigen; CMV: cytomegalovirus; TA-TMA: transplant-associated thrombotic microangiopathy.

DeLong test was used to compare the performance between two assays based on the AUC of receiver operating characteristics (ROC) curves. We obtained appropriate cut-off values and analyzed data according to the maximum value of the Youden index. Survival curves were performed using the Kaplan-Meier methodology and the log-rank test was used to compare variables. All variables with a P-value of less than 0.05 were considered statistically significant.

RESULTS

Patients

A total of 2858 children were admitted to the PICU from 2010 to 2019, and 131 received HSCT. The demographic characteristics of the patients are presented in Table 1. There were 63 boys (48.1%), and the median age of the patients admitted to the PICU was 11 years (interquartile range, 4–15 years). The most common underlying hemato-oncologic diagnosis was leukemia (n=67, 51.1%). A total of 104 (79.4%) allogeneic and 27 (20.6%) autologous bone marrow transplantation (BMT) procedures were performed. The median period from HSCT to admission was 197±84 days (0–3,658 days). The period from HSCT to admission was more than 100 days for 66.4% of the patients; 30–99 days, 17.6% and <30 days, 16%. The most commonly noted reasons for PICU admission was respiratory failure (n=58, 44.3%), followed by neurologic defects (n=18, 13.7%) and sepsis (n=17, 13.0%).

Demographics and Comparisons between Survivors and Non-survivors

The 28-day mortality rate was 22.1% (29/131). With respect to the baseline characteristics, the number of BMT and presence of septic shock were the significant factors affecting mortality (P=0.013 and P=0.031, respectively) (Table 1). As shown in Table 2, the severity of illness scores (OPRISM-III, PRISM-III, and pSOFA) and several laboratory values (serum lactic acid, and BNP level) at PICU admission were the significant prognostic factors. In terms of treatments administered within the first day of PICU admission, the use of MV and vasopressors was associated with mortality (P=0.011 and P=0.042, respectively).

Multivariate Logistic Regression Analysis

The result of univariate logistic regression was the same as the result of the comparison between survivors and non-survivors. However, in multivariate analysis adjusted for other potentially confounding independent variables, the number of HSCTs received (P<0.05), use of MV (P<0.05), OPRISM-III (odds ratio [OR], 1.137; 95% conficdence interval [CI], 1.074–1.204; P<0.001), PRISM-III (OR, 1.144; 95% CI, 1.0771.215; P<0.001) and pSOFA (OR, 1.222; 95% CI, 1.078–1.385; P=0.002) were independent predictors of PICU mortality in separate logistic equations (Table 3).

ROC Curve and Kaplan-Meier Analysis

We found that the value of the area under the ROC (AUROC) curve of the three severity of illness scores were all associated

Table 2. Laboratory values, severity of illness scores, and treatment on the first day of PICU

Variable	Total (n=131)	Survivor (n=102)	Non-survivor (n=29)	P-value
OPRISM-III	21.15±10.97	18.23±8.76	31.45±11.87	<0.001
PRISM-III	19.28±10.28	16.53±8.14	28.97±11.26	<0.001
pSOFA	7.24±3.99	9.06±3.57	12.38±4.56	0.001
Glasgow coma scale	10.66±4.46	1.57±1.48	2.21±1.86	0.097
Creatinine (mg/dl)	0.97±0.89	0.96±0.90	1.00±0.87	0.842
Total bilirubin (mg/dl)	2.47±6.42	2.21±6.93	3.38±4.15	0.390
Lactic acid (mmol/L)	3.79±3.93	2.79±2.73	7.31±5.31	<0.001
CRP (mg/dl)	11.85±11.78	11.47±11.32	13.26±13.45	0.478
BNP (pg/ml)	607.86±960.81	578.73±924.68	1,450.20±1,613.22	0.015
Use of mechanical ventilator	82 (62.6)	58 (56.9)	24 (82.8)	0.011
Use of vasoactive inotropic agents	51 (38.9)	35 (34.3)	16 (55.2)	0.042
Use of renal replacement therapy	36 (27.5)	27 (26.5)	9 (31)	0.627

Values are presented as mean±standard deviation or number (%).
PICU: pediatric intensive care unit; OPRISM-III: oncological pediatric risk of mortality-III; PRISM-III: pediatric risk of mortality-III; pSOFA: pediatric Sequential Organ Failure Assessment; CRP: C-reactive protein; BNP: B-type natriuretic peptide.

Table 3. Multivariate logistic regression analysis for the prediction of PICU mortality

Variable	Multivariate (model 1)		Multivariate (model 2)		Multivariate (model 3)	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
No. of HSCTs	3.368 (1.297–8.747)	0.013	3.045 (1.190–7.792)	0.02	3.532 (1.435–8.678)	0.006
Septic shock	0.794 (0.175–3.598)	0.765	1.028 (0.207–5.092)	0.973	0.917 (0.225–3.730)	0.903
OPRISM-III	1.142 (1.080–1.208)	<0.001				
PRISM-III			1.148 (1.082–1.218)	<0.001		
pSOFA					1.250 (1.109–1.409)	<0.001

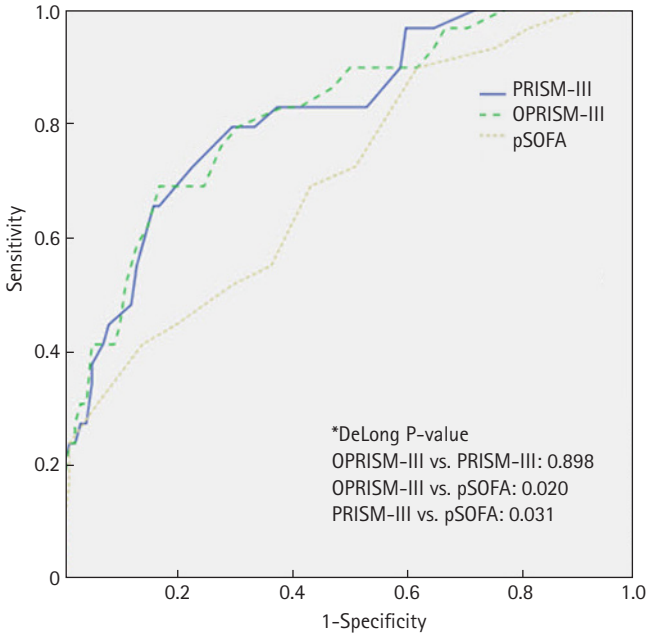
PICU: pediatric intensive care unit; HR: hazard ratio; CI: confidence incidence; HSCT, hematopoietic stem cell transplantation; OPRISM-III: oncological pediatric risk of mortality-III; PRISM-III: pediatric risk of mortality-III; pSOFA: pediatric Sequential Organ Failure Assessment.

with the 28-day mortality, and the AUC value of OPRISM-III score was the largest compared with other severity of illness scores (AUROC, 0.818; 95% CI, 0.731–0.905) (Figure 1). Using the DeLong test, the AUROC value of OPRISM-III and PRISM-III were significantly larger than that of pSOFA. However, there were no significant differences between OPRISM-III and PRISM-III. Then, we calculated the cut-off value of each score by using the AUC and obtained appropriate cut-off values. The cut-off value of OPRISM-III was 21.5, PRISM-III was 19.5, and pSOFA was 11. All scoring systems showed significant differences with respect to the cut-off values associated with the 28-day mortality in the Kaplan-Meier analysis (Figure 2).

DISCUSSION

Although there have been changes in conditioning regimen, immunosuppressive agents due to the complications after HSCT, the mortality that occurs after BMT is still high. According to the result of this study, when comparing the survivors and non-survivors, the number of HSCTs received, septic shock, use of inotropics and MV, severity of illness scores, serum lactic acid and BNP levels were associated with mortality in pediatric patients after HSCT. In multivariate analysis of 28-day mortality, the number of HSCTs done, OPRISM-III, PRISM-III, and pSOFA scores were the independent prognostic factors of 28-day mortality.

The number of HSCTs received and use of MV are already known predictors of mortality, based on previous studies [10,11,13,18-21]. The strength of our study was that the three scoring systems mentioned in each of the different studies are all significant predictors of mortality. Previous pediatric study, the OPRISM and PRISM-III were investigated for predicting mortality [22-27]. Another pediatric study reported that the difference between the maximum pSOFA and admission pSOFA scores was associated with the PICU mortality [28].



Variables	AUROC (95% CI)
PRISM-III	0.816 (0.730–0.903)
OPRISM-III	0.818 (0.731–0.905)
pSOFA	0.704 (0.596–0.812)

Figure 1. Receiver operating characteristics (ROC) curve and result of DeLong test between the area under the curve value of each scoring system. PRISM-III: pediatric risk of mortality-III; OPRISM-III: oncological pediatric risk of mortality-III; pSOFA: pediatric Sequential Organ Failure Assessment; AUROC: area under the receiver operating characteristics; CI: conficdence interval.

Our study differed from the previous pediatric study in that we evaluated the pSOFA score, a useful evaluation tool in recent pediatric critical care, together with OPRISM-III and PRISM-III on PICU admission. Therefore, three scoring systems were all useful tool to predict mortality of critically ill pediatric patients received BMT according to our study.

Previous studies showed that septic shock, use of vasoactive inotropes, and serum lactic acid were good predictors

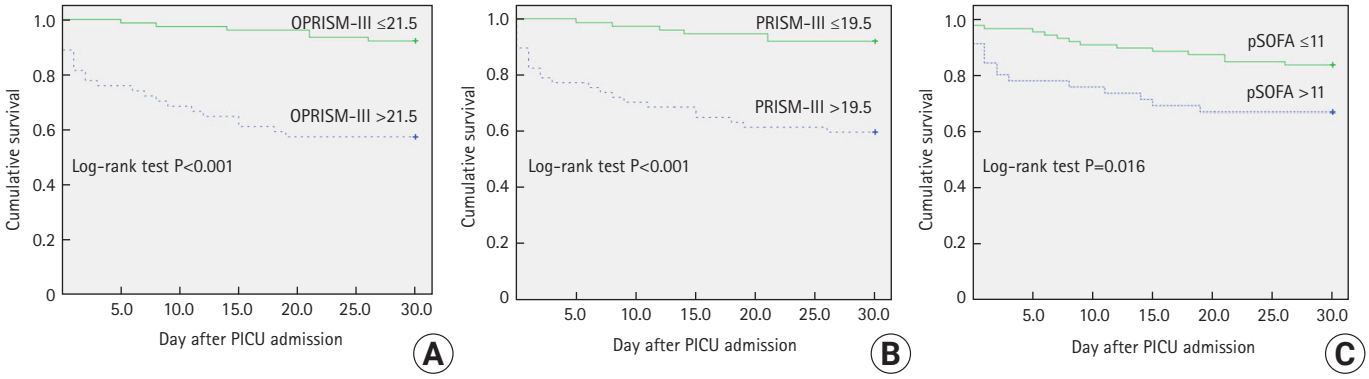


Figure 2. Kaplan-Meier analysis of oncological pediatric risk of mortality-III (OPRISM-III; A), pediatric risk of mortality-III (PRISM-III; B) and pediatric Sequential Organ Failure Assessment (pSOFA; C). All of these three scoring systems have significant difference in 28-day mortality. PICU: pediatric intensive care unit.

between survivors and non-survivors [10,18,23,29]. However, the GCS, creatinine, total bilirubin known mortality predictors in hildren after HSCT were not associated with mortality in our study [19,22,23,27,28,30,31]. When each organ failure is separately investigated, no correlation with the probability of mortality was seen in our study. However, the severity of illness scores at PICU admission, such as the pSOFA score, which includes the GCS score, creatinine, total bilirubin, that showed perfect discriminatory power for the evaluation of multi organ function adjusted for age were significantly higher among the non-survivors [16].

Previous studies have shown that septic shock to be a significant predictor of outcome in HSCT recipients admitted to the ICU [32,33]. In our study, septic shock was not significant factor by using multivariate logistic regression analysis. Because, most septic shock patients had effective response on early fluid therapy and vasopressor administration. Although septic shock is associated with an overall severe course, rapid recovery of specific organ function has been noted due to recent advances and improvements in the management of septic shock in cancer patients [34,35]. Early involvement in septic shock treatment represents that it had less effect on mortality than other organ complications. Rather, multi organ dysfunction on the first day after PICU admission were found to be more important than presence of septic shock at PICU admission.

Heart failure is a known complication of HSCT because of the use of cardiotoxic drugs post-transplantation, notably cyclophosphamide and anthracyclines [36,37]. Therefore, physicians often use BNP to monitor the cardiotoxic effects of medications after HSCT [38]. Although BNP may be a useful predictor of cardiac dysfunction after HSCT, it is not superior to other factors in predicting mortality. Even though we compensated for age-based creatinine levels, it has been confirmed that there is no association between creatinine level and BNP. In terms of vasopressors, several studies have shown that the use of vasopressors had a negative impact on survival in univariate analysis but was not significantly associated with mortality in multivariate analysis when compared with the severity of illness scores, such as APACHE II, SOFA, and OPRISM scores [11,21,23]. In our study, the severity of illness scores, such as PRISM-III and pSOFA scores, which included the systolic blood pressure (SBP) or MAP and the amount of vasoactive infusion as variables, were the independent prognostic factors of the 28-day mortality compared to the use of vasoactive inotropes. This result showed that the amount of inotropes and MAP or SBP before starting inotropes are more important factors for predicting the 28-day mortality in the PICU than the use of inotropes

There are some limitations of this study. This study was a retrospective single-center study, investigating only HSCT patients. Thus, the results cannot be generalized to all hemato-oncologic patients. It is necessary to study larger cohorts of HSCT patients from multiple centers. In conclusion, this study investigated the patients admitted to the PICU after HSCT at a single center. We found that the number of HSCTs received, use of MV, and the severity of illness scores (OPRISM-III, PRISM-III, and pSOFA scores) were the strong prognostic factors for PICU mortality in the critically-ill pediatric patients after HSCT.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Da Hyun Kim	https://orcid.org/0000-0002-8588-7848
Eun Ju Ha	https://orcid.org/0000-0002-2866-3848
Seong Jong Park	https://orcid.org/0000-0003-0250-2381
Kyung-Nam Koh	https://orcid.org/0000-0002-6376-672X
Hyery Kim	https://orcid.org/0000-0003-2852-6832
Ho Joon Im	https://orcid.org/0000-0001-8799-4068
Won Kyoung Jhang	https://orcid.org/0000-0003-2309-0494

AUTHOR CONTRIBUTIONS

Conceptualization: DHK, SJP, KNK, HK, HJI, WKJ. Formal analysis: DHK, WKJ, SJP. Methodology: DHK, WKJ, SJP, HJI. Data curation: DHK, EJH. Writing-original draft: DHK, WKJ. Writing-review & editing: SJP, WKJ.

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