The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

722.ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION

Development of a Stacked Ensemble Model for Risk Stratification of Chronic Gvhd after Allogeneic HSCT: Trump Cohort Study

Makoto Iwasaki, MDPhD[1], Junya Kanda, MD PhD[2], Fumihiko Kimura, MD PhD[3], Sachiko Seo, MD PhD[4], Yoshiko Atsuta, MD PhD[5], Naoyuki Uchida, MD PhD[6], Noriko Doki, MD PhD[7], Takahiro Fukuda, MD PhD[8], Tetsuya Nishida, MD PhD[9], Yuta Katayama, MD PhD[10], Masatsugu Tanaka, MD, PhD[11], Tetsuya Eto, MD PhD[12], Kazuhiro Ikegame, MDPhD[13], Yoshinobu Kanda[14], Masashi Sawa, MD PhD[15], Makoto Onizuka, MD PhD[16], Moeko Hino, MD PhD[17], Tatsuo Ichinohe, MDPhD[18], Ken Tabuchi, MD PhD[19], Akifumi Takaori-Kondo, MDPhD[20]

[1] Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Nara, Japan
[2] Department of Hematology, Kyoto University Hospital, Kyoto, Japan
[3] Division of Hematology, National Defense Med. College, Tokorozawa, JPN
[4] Department of Hematology and Oncology, Dokkyo Medical University,, Tochigi, JPN
[5] Japanese Data Center For Hematopoietic Cell Transplantation, Nagakute, Japan
[6] Department of Hematology, Toranomon Hospital, Tokyo, Japan
[7] Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan
[8] Department of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan
[9] Department of Hematology, Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital, Nagoya, Japan
[10] Department of Hematology, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Hiroshima, Japan
[11] Department of Hematology, Kanagawa Cancer Center, Kanagawa, Japan
[12] Department of Hematology, Hamanomachi Hospital, Fukuoka, JPN
[13] Department of Hematology, Hyogo Medical University Hospital, Nishinomiya, Japan
[14] Division of Hematology, Department of Medicine, Jichi Medical University, Tochigi, Japan
[15] Department of Hematology and Oncology, Anjo Kosei Hospital, Anjo, Japan
[16] Department of Hematology/Oncology, Tokai University School of Medicine, Isehara, Japan
[17] School of Medicine, Chiba University, Chiba, Japan
[18] Research Institute For Radiation Biology and Medicine, Hiroshima, Japan
[19] Japanese Data Center for Hematopoietic Cell Transplantation, Nagakute, Japan
[20] Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Background

Effective risk stratification is vital for selecting donors and developing treatment strategies for allogeneic hematopoietic stem cell transplantation (allo-HSCT). Several pretransplant risk models have been proposed to predict post-transplant patient outcomes from pretransplant risk factors. However, it is still challenging to predict mid-to-long-term prognosis. To establish a novel and user-friendly tool for predicting chronic graft-versus-host disease (cGVHD), non-relapse mortality (NRM) and overall survival (OS), we used a Stacked Ensemble Model (SEM) designed to handle right-censored data and competing risk events (Iwasaki et al., 2021).

Methods

Using Japanese registry data, the Japanese Transplant Registry Unified Management Program, we analyzed 21,840 patients who underwent their first allo-HSCT between 2010 and 2018 for hematologic malignancies. Of these, 14,430 patients were alive without cGVHD and relapse on day 100 post-transplantation. Primary endpoint was cGVHD and secondary endpoints were NRM and OS. Data were randomly split into the training set (70% of the dataset) and the validation set (30%). We treated patient age and time from diagnosis to transplant as continuous variables and performance status, ABO type matching, sex matching, disease/status groups based on refined Disease Risk Index, Hematopoietic Cell Transplantation-specific Comorbidity Index, usage of total body irradiation, conditioning intensity, T cell depletion in vivo, human leukocyte antigen (HLA) locus matching, the number of HLA mismatching and CMV serostatus as categorical variables. To evaluate predictive accuracy at day 30, 60 and 100 posttransplant, we considered acute graft-versus-host disease (aGVHD) and its treatment, including

grade 2 to 4 aGVHD occurrence, grade 3 to 4 aGVHD occurrence, stage of aGVHD before and after treatment, corticosteroid treatment, anti-thymocyte globulin treatment and treatment response of 1 st line therapy for aGVHD.

Results

The median age of the patients at transplantation was 51 years (inter quartile range (IQR): 39 - 60). The sources of stem cells were HLA-matched related bone marrow (BM) in 967 patients, HLA-matched related peripheral blood (PB) in 1,998 patients, haploidentical BM in 172 patients, haploidentical PB in 778 patients, unrelated BM in 5,539 patients, unrelated PB in 366 patients, and cord blood in 4,237 patients. Myeloablative conditioning was administered in 9,390 patients and reduced-intensity conditioning in 5,040 patients. The most common indication of HSCT was intermediate-risk acute myeloid leukemia (AML) in complete remission (CR, n=3,233) followed by acute lymphoblastic leukemia in first CR (n=2,164) and intermediate-risk AML in non-CR (n=1,618). Median follow-up period of survivors was 2.2 years (IQR: 0.9-4.5).

The overall performance of SEM was superior across the endpoints evaluated, cGVHD, NRM and OS, while XGBoost showed a slightly higher C-index for cGVHD, demonstrating its robustness and reliability (Table 1, the C-index for cGVHD/NRM/OS-SEM: 0.567/0.635/0.607, Cox-PH: 0.550/0.624/0.602, Random Survival Forest: 0.555/0.632/0.597, XGBoost: 0.573/0.624/0.604, and Dynamic Deephit: 0.549/0.614/0.589). C-index of SEM for cGVHD, NRM, and OS were gradually improved as time goes by (Table 1, the C-index for cGVHD/NRM/OS: at day 30-0.589/0.643/0.635, at day 60-0.598/0.655/0.640, at day 100-0.598/0.688/0.640).

Kaplan-Meier curves 100-day post-transplantation confirmed the accuracy of our predictions, effectively stratifying patients into four risk groups (Figure 1). SHapley Additive Explanations showed contribution of variables for predicting specific outcomes. Grade 3 to 4 aGVHD and stage of aGVHD after treatment influenced non-relapse mortality. Particularly, grade 3 to 4 aGVHD showed significant impact on OS in line with pretransplant risk factors including sex matching, donor source and disease/status groups. Grade 2 to 4 aGVHD and treatment response of 1 st line therapy for aGVHD influenced cGVHD.
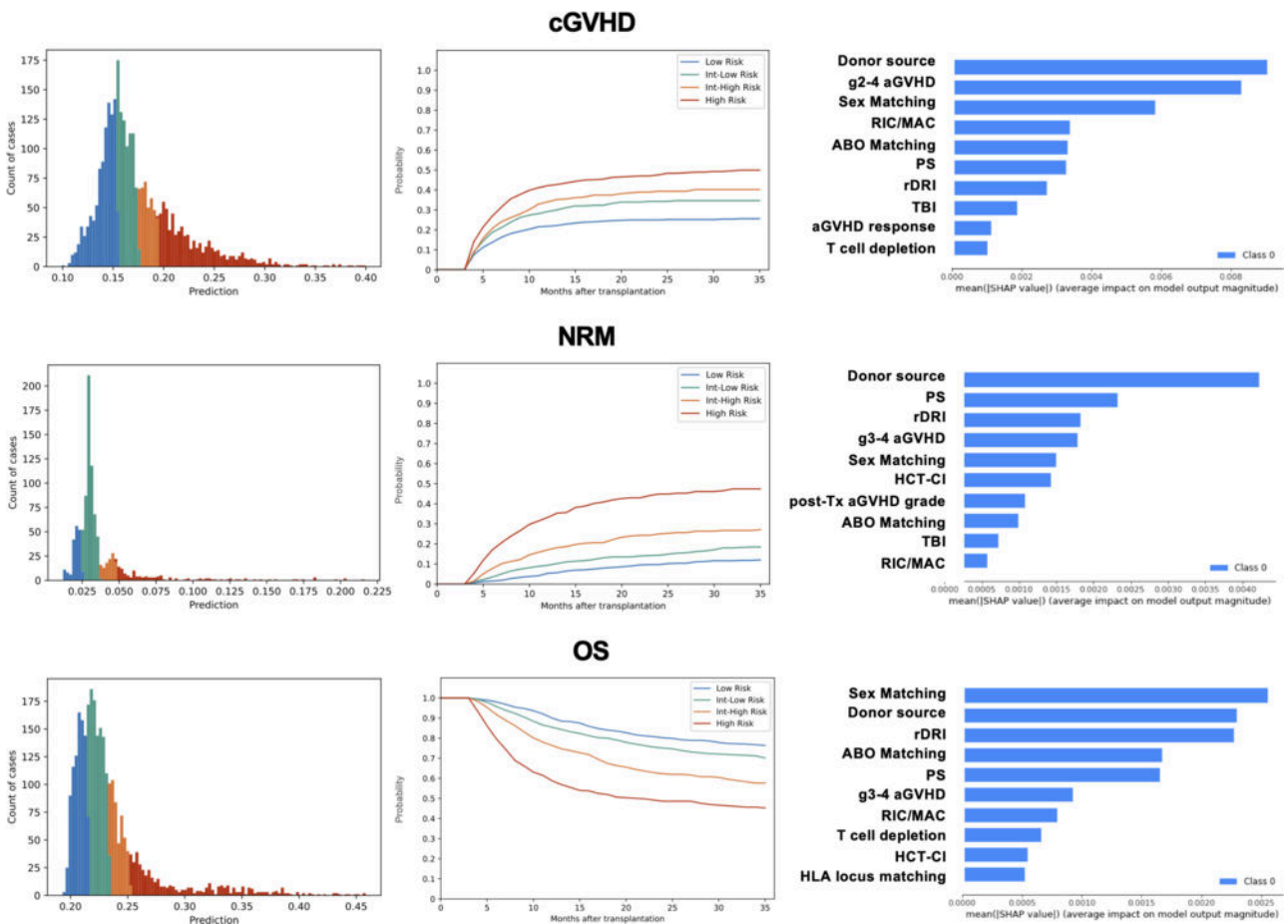
Conclusion

Our study emphasizes the importance of aGVHD events in mid-to-long-term post-transplantation outcomes and presents SEM-based prediction models that account for early-phase post-transplantation events. We are currently developing a user-friendly web application tool for cGVHD, aiming to enhance post-transplant risk stratification and preemptive therapy for cGVHD.

Table 1. Performance of each prediction model according to C-index in the validation cohort.

Estimator	cGVHD				NRM				OS			
	d0	d30	d60	d100	d0	d30	d60	d100	d0	d30	d60	d100
Stacked Ensemble	**0.567**	**0.589**	**0.598**	**0.598**	**0.635**	**0.643**	**0.655**	**0.688**	**0.607**	**0.635**	**0.640**	**0.640**
Dynamic Deephit	0.549	0.569	0.582	0.577	0.614	0.609	0.627	0.673	0.585	0.603	0.610	0.632
XGBoost	0.573	0.579	0.591	0.591	0.624	0.641	0.654	0.677	0.604	0.632	0.634	0.641
Cox-PH	0.550	0.565	0.578	0.581	0.624	0.612	0.634	0.675	0.602	0.614	0.627	0.636
Random Survival Forest	0.555	0.560	0.586	0.585	0.632	0.614	0.643	0.684	0.597	0.614	0.629	0.632

Figure 1. Predicted Value Distribution, Survival/Cumulative Incidence Curves, and mean SHAP values of top 10 variables for cGVHD, NRM and OS

Figure 1

https://doi.org/10.1182/blood-2023-173779