Interactive Web Application for Plotting Personalized Prognosis Prediction Curves in Allogeneic Hematopoietic Cell Transplantation Using Machine Learning

Hiroshi Okamura, MD, PhD,1 Mika Nakamae, MD, PhD,1 Shiro Koh, MD, PhD,1 Satoru Nanno, MD, PhD,1 Yasuhiro Nakashima, MD, PhD,1 Hideo Koh, MD, PhD,1 Takahiko Nakane, MD, PhD,1 Asao Hirose, MD, PhD,1 Masayuki Hino, MD, PhD,1 and Hirohisa Nakamae, MD, PhD1

INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is an advanced therapeutic intervention required for high-risk malignant hematological disorders.1 Various complex and intertwined pretransplant factors affect patient prognosis after allo-HCT.2-5 Transplant clinicians need to estimate individual prognosis after allo-HCT in clinical practice by combining not only certain indices that can stratify the prognosis after allo-HCT, such as refined Disease Risk Index (DRI-R), European Group for Blood and Marrow Transplantation (EBMT) risk score, and Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI), but also individual factors (eg, age, performance status [PS], disease status, or the number of transplantations) and transplant procedures (eg, donor source or conditioning regimen).6-8 However, the predictive capacities of these prognostic indices remain suboptimal.2 Furthermore, prognosis prediction based on the empirical integration of multiple patient-specific factors by the clinician is not always objective because of the complexity of allo-HCT treatment.

Background. Allogeneic hematopoietic cell transplantation (allo-HCT) is a curative treatment option for malignant hematological disorders. Transplant clinicians estimate patient-specific prognosis empirically in clinical practice based on previous studies on similar patients. However, this approach does not provide objective data. The present study primarily aimed to develop a tool capable of providing accurate personalized prognosis prediction after allo-HCT in an objective manner.

Methods. We developed an interactive web application tool with a graphical user interface capable of plotting the personalized survival and cumulative incidence prediction curves after allo-HCT adjusted by 8 patient-specific factors, which are known as prognostic predictors, and assessed their predictive performances. A random survival forest model using the data of patients who underwent allo-HCT at our institution was applied to develop this application. Results. We succeeded in showing the personalized prognosis prediction curves of 1-year overall survival, progression-free survival, relapse/progression, and nonrelapse mortality (NRM) interactively using our web application (https://predicted-os-after-transplantation.shinyapps.io/RSF_model/). To assess its predictive performance, the entire cohort (363 cases) was split into a training cohort (70%) and a test cohort (30%) time-sequentially based on the patients’ transplant dates. The areas under the receiver-operating characteristic curves for 1-year overall survival, progression-free survival, relapse/progression, and nonrelapse mortality in test cohort were 0.70, 0.72, 0.73, and 0.77, respectively. Conclusions. The new web application could allow transplant clinicians to inform a new allo-HCT candidate of the objective personalized prognosis prediction and facilitate decision-making.

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A random survival forest (RSF) is an ensemble machine learning method for right-censored time-to-event data analysis. Recently, RSF has become increasingly popular for survival data analysis in various medical fields because of its high-precision predictions.9–11 It is possible to develop a prognosis prediction model integrating multiple factors to compute patient-specific prognosis prediction curves such as survival or cumulative incidence adjusted for individual factors of a new patient using RSF.12 Although the most popular model for survival analysis is the Cox proportional hazard (Cox PH) regression, RSF has some advantages over the Cox PH model. First, RSF can easily deal with nonlinear effects, correlated parameters, and variable interaction. Second, although the Cox PH model may be limited due to the proportional hazards assumption, RSF is nonparametric and completely independent of model assumptions.11,13 Therefore, survival prediction analysis by RSF may provide novel insights into the allo-HCT field.

Although objective and accurate patient-specific prognosis prediction using a machine learning model can be quite informative for clinicians and patients in clinical decision-making, it has not been applied in a clinical setting. A user-friendly tool for constructing accurate personalized prognosis prediction curves after allo-HCT is lacking. Such a tool could allow transplant clinicians to inform patients of patient-specific prognosis prediction objectively derived from past patient data and build an optimal personalized treatment strategy.

Here, we developed a web application tool with a graphical user interface capable of plotting the personalized survival and cumulative incidence prediction curves after allo-HCT adjusted by 8 patient-specific factors, which are known as prognostic predictors, using RSF and assessed their predictive performances.

MATERIALS AND METHODS

Patients and Definition

This study, comprising retrospective prognostic modeling, analyzed a group of consecutive patients who underwent allo-HCT at our institution between January 2008 and November 2017. All pretransplant factors were recorded in the medical chart within 28 days before conditioning. The conditioning regimen containing either total body irradiation in fractionated doses ≥8 Gy, an oral busulfan dose of ≥9 mg/kg, or a melphalan dose of ≥140 mg/m² was defined as myeloablative in fractionated doses ≥8 Gy, an oral busulfan dose of ≥9 mg/kg, or a melphalan dose of ≥140 mg/m² was defined as myeloablative in line with a previous report.14 HLA compatibility was defined by DNA typing for HLA-A, HLA-B, HLA-C, and HLA-DR. This study was approved by the Ethical Committee of Osaka City University Graduate School of Medicine.

Supportive Care

Prophylactic antibiotics, either levofloxacin or polymyxin B oral tablets, an antifungal agent, and acyclovir were routinely administered from the start of conditioning. Trimethoprim-sulfamethoxazole was also administered from the start of conditioning to 2 days before allo-HCT and after neutrophil engraftment to prevent Pneumocystis jirovecii–induced pneumonia. Granulocyte colony-stimulating factor treatment was generally initiated from the day following allo-HCT to neutrophil engraftment. Ursodeoxycholic acid was administered from the start of conditioning to prevent sinusoidal obstruction syndrome.15

Predictors and Outcomes

Eight pretransplant factors, including recipients’ age, DRI-R, HCT-CI, PS, donor source (related bone marrow, related peripheral blood, unrelated bone marrow, cord blood, or haploidentical peripheral blood), HLA compatibility, conditioning intensity (myeloablative conditioning or reduced-intensity conditioning), and the number of allo-HCT, were used as prognostic predictors, which satisfied all following requirements:

- The generally well-known factors as prognostic predictors for allo-HCT.
- The factors that are obtained easily and inexpensively in most transplant institutes.
- The factors that affect prognosis after allo-HCT with uniform unit or scale regardless of underlying hematological disease.
- Intervventional prognostic factors that were preferentially selected because the better patient-specific treatment option might be able to be chosen using personalized prognosis prediction.

The predictive objectives were prediction of 1-year overall survival (OS), 1-year progression-free survival (PFS), and 1-year cumulative incidences of relapse/progression and nonrelapse mortality (NRM). An OS event was defined as death from any cause. PFS was defined as survival without relapse/progression. NRM was defined as death without relapse/progression. We considered cases that never achieved complete remission after allo-HCT as relapse/progression on day 1 after allo-HCT. Relapse/progression and NRM were treated as competing events with one another. The probabilities of OS and PFS were calculated using the Kaplan–Meier method. Cumulative incidences of relapse/progression and NRM were calculated using Gray’s method.

Statistical Analysis

The following is a summary of the analysis outline: (1) preprocessing data quality assurance, (2) development of a web application tool, and (3) assessment of the predictive performance for OS, PFS, relapse/progression, and NRM in accordance with the type 2b (nonrandom split-sample development and validation) of prediction model studies covered by the Transparent Reporting of a prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.16 We had no missing data. The number of trees to develop the RSF model was set as 500. A log-rank splitting rule was used to grow survival trees of a forest.

We used R package randomForestSRC for analysis of the RSF model, R package timeROC for calculating area under the receiver-operating characteristic curves (AUCs), and R package shiny/R for development of the web application.17,18 All analyses were performed using R version 3.5.1. We adhere to the TRIPOD statement.16

Performance Assessment of Predictive Model

All predictive performances were calculated using the time-dependent AUC.18 First, the entire cohort was split into a training cohort (70%) and a test cohort (30%) time-sequentially based on the patients’ transplant dates.
Second, the optimal number of variables randomly selected as candidates for splitting a node, which is a hyperparameter in the RSF model, for each outcome was tuned using 5-fold cross-validation method in the training cohort. It was defined as the one with the highest AUC value. Third, we assessed the predictive performances of the RSF, Cox PH model, DRI-R, and HCT-CI for 1-year OS and PFS and of RSF, DRI-R, and HCT-CI for 1-year relapse/progression and NRM in test cohort. We plotted time-sequential AUCs per month from 3 to 12 months after allo-HCT in the test cohort to assess the continuous predictive performances in each prognosis prediction curve. The schema of the assessment method for these predictive models is shown in Figure S1, SDC, http://links.lww.com/TP/B959.

Development of a Web Application Tool

We developed a web application tool capable of plotting the personalized prognosis prediction curves of 1-year OS, 1-year PFS, and 1-year cumulative incidences of relapse/progression and NRM adjusted by 8 patient-specific factors of a new allo-HCT candidate, using RSF predictive model trained by the entire cohort.

RESULTS

Patients and Transplantations

Three hundred eighty-four patients underwent allo-HCT. One patient who underwent transplant from unrelated peripheral blood stem cells was excluded due to insufficient sample for analysis. Because DRI-R cannot be scored when there is benign or rare disease, 21 patients were also excluded (11, aplastic anemia; 1, idiopathic cytopenia of undetermined significance; 4, chronic active Epstein–Barr virus disease; 1, plasma cell leukemia; 2, chronic myelomonocytic leukemia; 1, myelodysplastic/myeloproliferative neoplasms, unclassifiable; 1, natural killer cell lymphoblastic leukemia/lymphoma). In total, 363 patients were analyzed in this study. The clinical characteristics and outcomes in the training cohort (254/363), test cohort (109/363), and entire cohort are listed in Table 1. This study. The clinical characteristics and outcomes in the training cohort (254/363), test cohort (109/363), and entire cohort are listed in Table 1.

Interactive Web Application for Plotting Personalized Prognosis Prediction Curves

The interactive web application that shows the personalized 1-year prognosis prediction curves after allo-HCT is shown in Figure 1. Users choose an outcome they intend to predict among OS, PFS, relapse/progression, or NRM in the select box at left-top (a). Next, after users set 8 patient-specific factors in the left side-panel (b) and click the “prediction” button (c), the personalized 1-year prognosis prediction curve is displayed in the main panel (d). For example, Figure 1 shows the personalized 1-year OS prediction curve after allo-HCT for a patient whose 8 pretransplant factors are as follows: age, 50; DRI-R, high; PS, 1; HCT-CI, 1; conditioning intensity, myeloablative conditioning; HLA compatibility, matched; donor source, related peripheral blood; the number of allo-HCT, 1. This patient’s 1-year OS rate after allo-HCT is predicted at 59.1%. Users can also see the personalized 1-year PFS curve and cumulative incidence prediction curves of relapse/progression and NRM after allo-HCT. We provided an online interface to use this web application (https://predicted-os-after-transplantation.shinyapps.io/RSF_model/) and its

### Table 1. Patient characteristics

| Characteristic | Training cohort (n = 254) | Test cohort (n = 109) | Entire cohort (n = 363) |
|---------------|--------------------------|----------------------|------------------------|
| Median age (range) | 46 (17–69) | 48 (18–68) | 46 (17–69) |
| Diagnosis (%) | | | |
| AML | 111 (44) | 59 (54) | 170 (47) |
| ALL | 47 (19) | 16 (15) | 63 (17) |
| MDS | 35 (14) | 11 (10) | 46 (13) |
| CML | 10 (4) | 3 (3) | 13 (4) |
| ML | 30 (12) | 13 (12) | 43 (12) |
| Others | 21 (8) | 7 (6) | 28 (8) |
| DRI-R (%) | | | |
| Low | 12 (5) | 7 (6) | 19 (5) |
| Int | 132 (52) | 44 (40) | 176 (49) |
| High | 89 (35) | 41 (38) | 130 (36) |
| Very high | 21 (8) | 17 (16) | 38 (11) |
| HCT-CI (%) | | | |
| 0 | 102 (40) | 45 (41) | 147 (41) |
| 1 | 42 (17) | 25 (23) | 67 (19) |
| 2 | 41 (16) | 21 (19) | 62 (17) |
| ≥3 | 69 (27) | 18 (17) | 87 (24) |
| Conditioning (%) | | | |
| MAC | 183 (72) | 36 (33) | 219 (60) |
| RIC | 71 (28) | 73 (67) | 144 (40) |
| HLA disparity (%) | | | |
| Matched | 109 (43) | 30 (28) | 139 (38) |
| Mismatched | 145 (57) | 79 (73) | 224 (62) |
| Source of stem cell (%) | | | |
| rBM | 6 (2) | 2 (2) | 8 (2) |
| rPB | 41 (16) | 13 (12) | 54 (15) |
| uBM | 89 (35) | 18 (17) | 107 (30) |
| CB | 60 (24) | 20 (18) | 80 (22) |
| Haplo PB | 58 (23) | 56 (51) | 114 (31) |
| PS (%) | | | |
| 0 | 123 (48) | 62 (57) | 185 (51) |
| 1 | 116 (46) | 43 (39) | 159 (44) |
| ≥2 | 15 (6) | 4 (4) | 19 (5) |
| Number of allo-HCT (%) | | | |
| 1 | 208 (82) | 81 (74) | 289 (80) |
| 2 | 38 (15) | 24 (22) | 62 (17) |
| 3 | 8 (3) | 4 (4) | 12 (3) |
| Year of allo-HCT (%) | | | |
| 2008–2014 | 251 (99) | 0 (0) | 251 (69) |
| 2015–2017 | 3 (1) | 109 (100) | 112 (31) |
| Outcome (95% CI) | | | |
| 1-y OS (%) | 62.5 (66.2-68.1) | 63.3 (63.4-71.7) | 62.7 (57.5-67.5) |
| 1-y PFS (%) | 51.2 (49.5-57.1) | 54.7 (52.6-54.8) | 49.6 (44.3-54.6) |
| 1-y relapse/progression (%) | 39.0 (33.0-44.9) | 44.2 (34.6-53.3) | 40.5 (35.4-45.5) |
| 1-y NRM (%) | 9.8 (6.6-13.9) | 10.1 (5.3-16.6) | 9.9 (7.1-13.3) |
| Median follow-up mo for the survivor (range) | 72.0 (8.1–127.9) | 20.1 (2.4–41.8) | 51.9 (2.4–127.9) |

ALL, acute lymphoblastic leukemia; allo-HCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; CB, cord blood; CI, confidence interval; CML, chronic myeloid leukemia; DRI-R, refined Disease Risk Index; HCT-CI, Hematopoietic Cell Transplantation Comorbidity Index; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; ML, malignant lymphoma; NRM, nonrelapse mortality; OS, overall survival; PB, peripheral blood; PFS, progression-free survival; PS, performance status; rBM, related bone marrow; RIC, reduced intensity conditioning; rPB, related peripheral blood; uBM, unrelated bone marrow.
The predictive performance for each 1-year prognosis model in the RSF trained by the entire cohort is shown in Table S1, SDC, http://links.lww.com/TP/B959. They were calculated using the 5-fold cross-validation method to prevent overfitting.

**Assessment of Predictive Performance**

The AUCs calculated by the 5-fold cross-validation in the training cohort for 1-year OS, PFS, relapse/progression, and NRM per hyperparameter in the RSF model are shown in Table S2, SDC, http://links.lww.com/TP/B959. The optimal number of variable candidates for splitting a node in the RSF model for 1-year OS, PFS, relapse/progression, and NRM was 7, 2, 2, and 5, respectively.

The AUCs for 1-year OS, PFS, relapse/progression, and NRM in the test cohort were 0.70, 0.72, 0.73, and 0.77, respectively. On the whole, the predictive performance of RSF was consistently high throughout every outcome compared with other prognostic scores such as DRI-R, HCT-CI, hematopoietic cell transplant-composite risk, HCT-CI/Age index, or EBMT risk score (Table S3, SDC, http://links.lww.com/TP/B959).6-8,20,21 Time-sequential AUCs plotted per month from 3 to 12 months after allo-HCT for OS, PFS, relapse/progression, and NRM in the test cohort are shown in Figure 2. The predictive performances of RSF for OS and PFS were comparable to those of the Cox PH model at any time-point. The predictive performances of RSF for every outcome were superior to those of DRI-R or HCT-CI alone consistently at any given time-point.

We performed further analysis to explore the patient number of the training cohort required to keep the predictive performance of our RSF model high. The patients of the training cohorts in this analysis were randomly extracted from the entire training cohort (254 cases) and were increased gradually from 42 to 254 cases. We assessed the AUCs of the RSF model developed by the training cohorts in each patient number using the test cohort (109 cases) and plotted them (Figure S2, SDC, http://links.lww.com/TP/B959). The greater the patient number of the training cohort was, the higher AUCs for both OS and PFS became. The AUCs for OS and PFS reached a plateau roughly when the patient number of training cohort was about >150.
DISCUSSION

We succeeded in developing an interactive web application tool with graphical user interface capable of accurately, objectively, and rapidly generating the 4 types of personalized 1-year prognosis prediction curves after allo-HCT in just a few steps using machine learning. To the best of our knowledge, there have been no previous reports regarding the development of a similar interactive tool that can provide various types of patient-specific prognosis prediction curves in allo-HCT.

Some predictive indices of prognosis after allo-HCT such as DRI-R, HCT-CI, EBMT risk score, and pretransplantation assessment of mortality score have been reported.\textsuperscript{2,6-8,22} Although these indices can stratify prognosis after allo-HCT, transplant clinicians need to empirically consider various additional factors, such as age, PS, donor source, or conditioning regimen, to estimate patient-specific prognosis in clinical practice. Our web application tool can calculate and plot personalized prognosis prediction curves more objectively than a clinician’s empirical estimate and more accurately than any single prognosis index.

Shouval et al\textsuperscript{23} developed a website to predict prognosis after allo-HCT using the alternating decision tree (ADTree), which is a machine learning model. Users can obtain personalized prognostic predictive information such as day 100 mortality by providing certain individual pretransplant factors for a new transplant candidate. However, the ADTree model cannot treat time-to-event data, whereas the RSF is a machine learning algorithm for survival analysis that can take the right-censored data or competing risks into consideration.\textsuperscript{12,24} Hence, our web application can not only provide prognosis prediction value for a fixed time point but also plot continuous survival and cumulative incidence prediction curves until 1 year after allo-HCT.
allo-HCT (Figure 1). Moreover, users can simulate various transplant settings for a particular patient intuitively with just a few clicks using mobile devices, such as tablets and smartphones, as well as computers, because our web application was developed using shiny/R library to ensure interactivity. Consequently, our web application can help transplant clinicians inform a new allo-HCT candidate of their personalized prognosis estimate in clinical practice, and it can provide both the clinician and candidate with valuable information to help make clinical decisions.

Shouval et al\textsuperscript{13,25} also reported on the prognosis prediction performance after allo-HCT by ADTree using registry data in EBMT and Italian Group for Bone Marrow Transplantation and showed that the time-dependent AUCs for 2-year OS were 0.66 and 0.65, respectively. Their prediction model developed using large amounts of patient data is quite relevant, because it can be used widely as a generalized prediction model in allo-HCT fields. However, various biases related to transplant institutes or countries are inherent in allo-HCT. For example, there are differences in the indications for allo-HCT, transplant experiences, patient characteristics, and strategy for donor source selection, conditioning regimen, or transplant-related complications among the transplant institutes or countries. Therefore, some reports have shown that there is a significant difference in prognosis after allo-HCT among transplant centers or countries.\textsuperscript{26,27} The prediction model developed using data from a single institution is protected from bias based on the differences among the transplant institutes as long as it is used within that institute, because the patient characteristics or transplant procedures similar to those of the training cohort by which the prediction model was developed are likely to be inherited by future patients at that institute. Furthermore, the noise of data collected from a single institute may be less than that of multicenter data, because the methods of clinical assessment or data collection could be consistent in a single institute. Hence, an in-house developed prognosis prediction model may have more advantages for prognosis predictive performance after allo-HCT in a particular institute than the prediction model based on data sourced from multiple institutions. Supporting this idea, Fuse et al\textsuperscript{28} also showed that the predictive performance of relapse in a single institute in which the predictive model was developed using ADTree was better than that in another institute using the identical predictive model (AUC: 0.75 versus 0.67). We have published the source code of our web application on the Internet. Each transplant center can also develop a web application using an in-house prognosis prediction model with its past patient data.

To assess the predictive performance, we developed predictive models with the training cohort, which is the former group generated by splitting the entire cohort into 2 groups time-sequentially, and their predictive performances were assessed in the test cohort, the latter group. This assessment method accords with the type 2b of prediction model studies covered by the TRIPOD statement.\textsuperscript{16} As a result, the predictive performances for 1-year OS, PFS, relapse/progression in the test cohort were worse than those in the training cohort (Tables S2 and S3, SDC, http://links.lww.com/TP/B959). These results could be attributed to the difference in the year of allo-HCT between the training and test cohorts. The predictive performance of the RSF model trained by the entire cohort, which was used in the web application, is shown in Table S1, SDC, http://links.lww.com/TP/B959. However, the predictive performances for the new allo-HCT candidates in this web application may not be as high as those shown in Table S1, SDC, http://links.lww.com/TP/B959 because the allo-HCT procedures and patient characteristics can change over time.

This study has several limitations. First, our web application is preliminary, and its predictive performance for new allo-HCT candidates in other institutes is not guaranteed because our model has not obtained external validation. If it is intended to use this web application widely in other transplant institutes, it will be required to confirm its prediction performance in advance by multicenter research. Second, as a retrospective analysis, this web application may be susceptible to selection bias, which may limit the interpretation of the prediction results. Third, there may be other combinations of pretransplant factors that are better for prognosis prediction. We could not help restricting the number of pretransplant predictors to 8 to ensure the usability of this web application tool. Further studies on the variable selection are required to improve predictive performance. Fourth, the cases who were transplanted using unrelated peripheral blood stem cell, whose underlying disease was nonmalignant, or who were pediatric, could not be included in our predictive model for the reasons such as no or small sample size. Consequently, personalized prognosis prediction in these cases is impossible in our web application. Finally, when the patient number of training cohort to develop our predictive model was >150, AUCs for OS and PFS reached a plateau roughly (Figure S2, SDC, http://links.lww.com/TP/B959). However, it is inappropriate that this finding is extrapolated to other institutes. We recommend that the patient number of the training cohort required to keep predictive performance plateau will be calculated in each institute in which the RSF model will be developed.

In conclusion, we developed an interactive web application tool capable of plotting 4 kinds of personalized prognosis prediction curves after allo-HCT objectively through the integration of 8 pretransplant factors using RSF and confirmed their promising predictive performances. The predictive information obtained by this web application could allow transplant clinicians to inform a new allo-HCT candidate of their objective personalized prognosis prediction in clinical practice and could support the clinician’s and the candidate’s decision-making.

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