Personalized timing for allogeneic stem-cell transplantation in hematologic neoplasms: a target trial emulation approach using multistate modeling and microsimulation

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Personalized Timing for Allogeneic Stem-Cell Transplantation in Hematologic Neoplasms: A Target Trial Emulation Approach Using Multistate Modeling and Microsimulation

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DOI https://doi.org/10.1200/CCI.23.00205

ABSTRACT

PURPOSE Decision about the optimal timing of a treatment procedure in patients with hematologic neoplasms is critical, especially for cellular therapies (most including allogeneic hematopoietic stem-cell transplantation [HSCT]). In the absence of evidence from randomized trials, real-world observational data become beneficial to study the effect of the treatment timing. In this study, a framework to estimate the expected outcome after an intervention in a time-to-event scenario is developed, with the aim of optimizing the timing in a personalized manner.

METHODS Retrospective real-world data are leveraged to emulate a target trial for treatment timing using multistate modeling and microsimulation. This case study focuses on myelodysplastic syndromes, serving as a prototype for rare cancers characterized by a heterogeneous clinical course and complex genomic background. A cohort of 7,118 patients treated according to conventional available treatments/evidence across Europe and United States is analyzed. The primary clinical objective is to determine the ideal timing for HSCT, the only curative option for these patients.

RESULTS This analysis enabled us to identify the most appropriate time frames for HSCT on the basis of each patient's unique profile, defined by a combination relevant patients' characteristics.

CONCLUSION The developed methodology offers a structured framework to address a relevant clinical issue in the field of hematology. It makes several valuable contributions: (1) novel insights into how to develop decision models to identify the most favorable HSCT timing, (2) evidence to inform clinical decisions in a real-world context, and (3) the incorporation of complex information into decision making. This framework can be applied to provide medical insights for clinical issues that cannot be adequately addressed through randomized clinical trials.

ACCOMPANYING CONTENT

Article, 10.1200/JCO.23.02175

Appendix

Accepted February 23, 2024
Published May 9, 2024

JCO Clin Cancer Inform
8:e2300205

INTRODUCTION

In the realm of clinical decision making, determining the optimal timing for interventions is crucial, especially when curative treatments are one-time events (such as cellular therapies in patients with hematologic neoplasms), necessitating a careful assessment of waiting time on the basis of the risk of treatment toxicity/failure and of disease progression. Additionally, the assumption of uniform treatment effects across populations often does not apply to timing, which demands individualized adjustments on the basis of patient characteristics. This is even more evident for rare diseases with heterogeneous clinical and genomic background. Although randomized trials are the reference source for providing clinical evidence, practical or ethical constraints can prevent them; in such instances, observational data play a crucial role in studying the effects of timing on treatment outcomes.[1-4]

In this work, observational data are exploited to address the challenge of identifying an optimal timing for allogeneic hematopoietic stem-cell transplantation (HSCT), which is the only curative option for most hematologic neoplasms. In the clinical setting of rare diseases with heterogeneous clinical outcomes, where the possibility to generate clinical evidence is hampered by the reduced data availability and by the complex biologic and clinical landscape, the need to develop

CONTEXT

Key Objective

How can decision models be developed to determine the timing of allogeneic hematopoietic stem-cell transplantation (HSCT) for hematologic neoplasms in an individualized way?

Knowledge Generated

Using real-world data, it is possible to address the clinical challenge of studying the optimal timing of HSCT in hematology with a target trial emulation approach on the basis of multistate modeling and microsimulation, enabling more effective personalized treatment strategies.

Relevance *(J.L. Warner)*

HSCT is a highly toxic therapy with efficacy critically dependent on timing. This study demonstrates that a data-driven approach to personalized timing is feasible for myelodysplastic syndromes and may be generalizable to other hematologic malignancies.*

*Relevance section written by *JCO Clinical Cancer Informatics* Editor-in-Chief Jeremy L. Warner, MD, MS, FAMIA, FASCO.

innovative methods to guide clinical decisions is maximized. This article specifically focuses on myelodysplastic syndromes (MDS),[5] rare hematologic neoplasms most occurring in the elderly, characterized by peripheral blood cytopenia and increased risk of evolution into AML. Patients with MDS present large clinical heterogeneity and outcome, and therefore a risk-adapted treatment strategy is needed.[6]

Clinical decision-making process in MDS relies on clinical parameters and biomarkers, which are synthesized in the Revised International Prognostic Scoring System (IPSS-R).[7] The IPSS-R has been recently refined and complemented by introducing genomic features that are closer to the disease biology and better define individual probability of survival and risk of disease progression (Molecular-International Prognostic Scoring System [IPSS-M]).[8]

HSCT is the only potentially curative treatment for patients with MDS.[9] However, it carries a significant risk of failure because of toxicity and disease relapse. Both pre- and post-HSCT survival depends on the timing of the procedure and patient-specific characteristics. Therefore, tailoring the timing of HSCT to eligible patients becomes essential for optimizing the procedure's effectiveness and clinical outcome.[10,11] The clinical challenge consists in planning, at the time of MDS diagnosis, when to perform HSCT on the basis of the available patient information.

In this study, a new method for optimizing the personalized timing of a treatment procedure (HSCT) exploiting observational data from an international multicenter longitudinal registry is developed. The proposed methodology emulates a target trial that randomly assigns eligible individuals into procedures given by different timing of intervention. Following the target trial emulation approach recently proposed by Hernán and Robins,[12] the essential design and analytical components of the study are meticulously established before conducting the analysis. Once the target protocol is defined, the clinical problem is translated into statistical terms by developing a tailored decision-strategy analysis for each patient profile of interest.

Patient profiles are delineated by key factors selected according to their clinical relevance in the decision-making process (for MDS: age and IPSS-R/IPSS-M).[7,8] The aim is to identify the optimal policies by computing the quality-adjusted average survival times using different transplantation policies and comparing them within each patient profile. For this reason, a multistate modeling framework is used to consider pre- and post-treatment disease states, adjusting for possible confounders on the timing of therapeutic procedure and post-treatment outcomes. This multistate *disease model* describes the natural history of the disease and estimates the effect of the covariates of interest. Finally, a *decision-strategy model* on the basis of microsimulation[13] is implemented to identify the optimal timing of the procedure associated with the highest survival time.

The main objective of the study is to delve into the statistical methodology. For this reason, here, the focus is on the conventional tool for treatment decision-making process in MDS (IPSS-R).[7] Detailed clinical results obtained after introducing patient genomic profile as assessed by IPSS-M[8] are discussed elsewhere.[14]

METHODS

Target Trial Emulation

The study was conducted by GenoMed4All[15] and Synthema[16] consortiums, with the support of EuroBloodNET, the European Reference Network on Rare Hematological Diseases,[17]

and of the International Consortium on MDS. The Humanitas Ethics Committee approved the study (ClinicalTrials.gov Identifier: NCT04889729). Informed consent was obtained from each participant.

Data from these consortiums were used to emulate a target trial for individuals diagnosed with MDS that incorporates random assignment among various treatment strategies on the basis of different HSCT timings. To emulate a target trial, the identification of a comprehensive protocol that outlines the fundamental design and analytical elements of the study (ie, eligibility criteria, treatment strategy, assignment procedures, outcomes, follow-up period, causal contrast of interest, and statistical analysis)[12,18] was necessary. A summary of the components of the emulated trial's protocol is given in Table 1.

Notation and Estimand of Interest

A multistate process with MDS pre-HSCT, AML pre-HSCT, post-HSCT, and post-HSCT and relapse as transient states, and death as final absorbing state was considered. Let Y_t denote the state of an individual at time $t \geq 0$. Let D be the time at which the death state is reached. Let C be the time to censoring, assumed to be noninformative. The observation time of the terminal event was $Y^D = \min(D, C)$. Moreover, the event indicator for reaching the absorbing state was $\delta^D = I(Y^D = D)$.

An intervention g on the timing to the treatment T was defined according to a distribution $g = G(T)$, where $g = G(\cdot)$ denoted a random draw for this distribution. Such distribution was assumed to be an arbitrary distribution chosen by the investigator. $D^{(g)}$ was defined as the potential timing for the terminal event under intervention g.

The interest was in estimating the expected conditional outcome after the intervention g on a subset of the vector X of observable covariates, denoted as X_1. The choice of the expected conditional outcome instead of a marginal one was made to obtain a tailored estimate for specific subpopulations defined by the vector X_1. In the considered application, the vector X contained the covariates of interest for the definition of the profiles, and the possible confounding factors. As measure of effect, the quality-adjusted restricted mean survival time (QA-RMST) on a time horizon was chosen, accounting for quality of life through the definition of the utility function h(•): $\text{QA} - \text{RMST}^{g}_{x_1} = E[\text{h}(\min(D^{(g)}, w)) | X_1 = x_1]$.

The timing of the intervention was defined to be continuous so that the QA-RMST defined above, given x_1, is a curve. Let $[t_1; t_2]$ denote the closed interval during which the intervention can take place. The final aim was to determine $t^*_{x_1} = \max_{g = t \in [t_1; t_2]} \text{QA} - \text{RMST}^{g=t}_{x_1}$, which was the time point in $[t_1; t_2]$ for which the outcome after intervention is maximum, conditionally on covariates X_1.

To identify the causal contrasts involving the potential outcome $D^{(g)}$, the main assumptions for causal inference (ie,

TABLE 1. Summary of the Protocol Components of a Target Trial to Study the Timing of HSCT Conditional on Patients' Profile in MDS

Protocol Component	Target Trial	Emulation Using Observational MDS Data
Eligibility criteria: Who will be included in the study?	Individuals ≥18 years diagnosed with MDS with IPSS-R risk score as low or higher	Same as for target trial Required data for each person: age, IPSS-R, history of MDS diagnosis
Treatment strategies: What interventions will eligible persons receive?	Different treatment strategies correspond to different timing of HSCT HSCT will be performed if the participants are still alive at the time assigned by the strategy, unless they have progressed to AML	Same as for target trial Required data for each person: date of HSCT, history of AML
Assignment procedures: How will eligible persons be assigned to the interventions?	Eligible participants will be randomly assigned to the different strategies and will be aware of the strategy to which they have been assigned	Eligible persons will be assigned to the strategies with which their data are compatible
Outcomes: What outcomes in eligible persons will be compared among intervention groups?	Conditional QA-RMST with respect to patient profile in terms of IPSS-R and age over a horizon of 8 years taking into account possible development of AML before HSCT and relapse after transplant	Same as for target trial (multistate outcome) Required data for each person: date of death during the study, history of AML, history of relapse
Follow-up period: During which period will eligible persons be followed in the study?	Starts at diagnosis of MDS and ends at death, loss at follow-up, or administrative end of the study	Same as for target trial Required data for each person: date of loss to follow-up
Causal contrasts of interest: Which counterfactual contrasts will be estimated using the above data?	Intention-to-treat effect (effect of being assigned to treatment)	Observational analog of the intention-to-treat effect
Statistical analysis: How will the counterfactual contrasts be estimated?	Intention-to-treat analysis via comparison of QA-RMST among individuals assigned to each HSCT timing strategy	Same as intention-to-treat analysis Required data for each person: history of AML, date of death, history of disease-modifying therapy

Abbreviations: HSCT, allogeneic hematopoietic stem-cell transplantation; IPSS-R, Revised International Prognostic Scoring System; IPSS-M, Molecular-International Prognostic Scoring System; MDS, myelodysplastic syndromes; QA-RMST, quality-adjusted restricted mean survival time.

consistency, conditional exchangeability, and positivity) must hold.[19]

Disease Model

To estimate the outcome after intervention g, it was necessary to estimate the transition hazards of the *disease model*. This required assessing the risk of death both before and after intervention, also considering the intermediate events; AML before HSCT and relapse after HSCT. The model was assumed to be semi-Markov, that is, a clock-reset time scale was used.[20] The model structure is shown in Figure 1: HSCT was considered possible only from MDS pre-HSCT in accordance with the target protocol (Table 1). The intervention aimed at controlling the intensity of transition from MDS pre-HSCT to post-HSCT (transition 2). This necessitated the estimation of all the other transition hazards from the data. For each transition, a cause-specific transition model was fitted using flexible parametric survival models as proposed by Royston and Parmar,[21] where IPSS-R[7] and age were used as covariates and the baseline hazards were modeled using restricted cubic splines. For the transitions from post-HSCT state, time of entry in the state was also included as an additional covariate. Model selection in terms of number of knots for the baseline hazards, possible inclusion of nonlinear effect for continuous variables, interactions between variables, and time-dependent effects was performed according to the lowest Bayesian information criteria. To ensure *conditional exchangeability* for observed covariates not contained in X_1, the transition hazards from post-HSCT needed to be estimated using either G-estimation or the inverse probability of treatment weighting (IPTW). Here, an IPTW setting was considered, while the estimation using G-estimation has been described elsewhere[22] (Appendix 1).

Decision-Strategy Model Through Microsimulation

Microsimulation was used to obtain the estimates of the QA-RMST under the intervention g. In general, microsimulation consists of simulating individuals' life trajectories from a specified multistate continuous time model using random-number generator.[23] Here, it allowed to mimic the target trial and evaluate what would occur if HSCT were performed at different time points. In the microsimulation, the only deterministic transition was the one from pre-HSCT and MDS to post-HSCT as it was dictated by the intervention g. All the others were stochastic, and they were defined by the ones estimated from the data using the *disease model* as previously described. For each individual with covariate vector x_1 assigned to a treatment strategy $g = t \in [t_1; t_2]$, its path through the multistate model over a time horizon w was simulated according to the microsimulation algorithm[23] reported in the Appendix 1. Finally, the estimates of the expected conditional QA-RMST under each scenario t and horizon w were computed by averaging the survival time across the simulated patients with the same values in the covariates x_1.

To provide a reliable decision analysis tool, the uncertainty in the estimations was considered by constructing confidence intervals. In the context of microsimulation, this can be done using probability sensitivity analysis (PSA)[24] on the basis of parametric bootstrap. When performing PSA, the parameters were considered random quantities themselves that were to be drawn from the asymptotic normal distribution of the maximum likelihood estimator. Therefore, in the microsimulation with PSA, first a random sample of B values for the vector of the parameters was generated. Then, for each parameter vector drawn, the microsimulation was performed, thus obtaining a vector of B estimates of QA-RMST for each scenario t and patient profile.

Decision-Strategy Analysis and Identification of Optimal Rules

In the case of microsimulation without uncertainty analysis, for each combination of the covariates X_1, a discrete set of points $(t, \widehat{RMST}_{x_1}^{g=t})$, that is, a set of treatment timings and

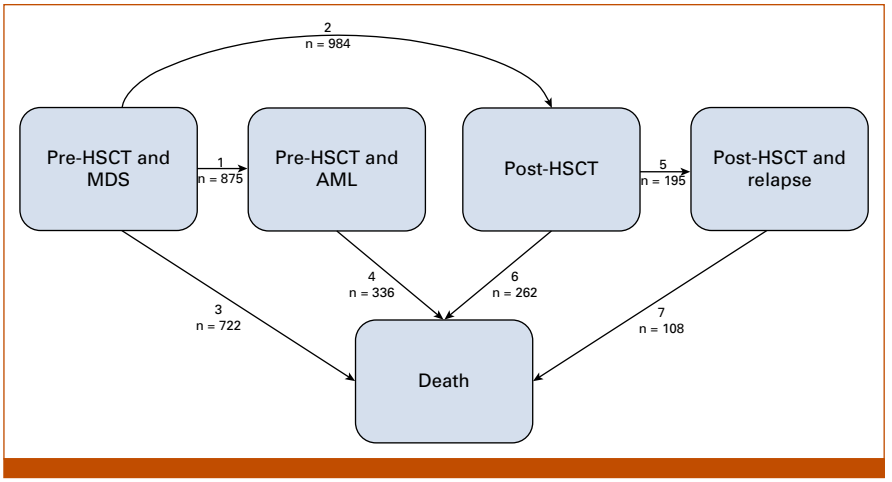

FIG 1. Multistate model structure and observed number of transitions in the training cohort. HSCT, allogeneic hematopoietic stem-cell transplantation; MDS, myelodysplastic syndromes.

TABLE 2. Results of the Multistate Disease Model

	Transition[a]					
	1: MDS → AML		3: MDS → Death		4: AML → Death	
Parameter	Coef (SE)	95% CI	Coef (SE)	95% CI	Coef (SE)	95% CI
Baseline hazard						
Gamma0 ($\widehat{\gamma_0}$)	−13.994 (0.643)	−15.254 to −12.733	−15.313 (0.439)	−16.174 to −14.452	−6.857 (0.774)	−8.374 to −5.340
Gamma1 ($\widehat{\gamma_1}$)	1.718 (0.132)	1.459 to 1.976	1.416 (0.037)	1.344 to 1.489	0.689 (0.275)	0.15 to 1.227
Gamma2 ($\widehat{\gamma_2}$)	0.015 (0.003)	0.009 to 0.022	—		−4.755 (0.671)	−6.071 to −3.44
Gamma3 ($\widehat{\gamma_3}$)	—		—		6.293 (0.882)	4.565 to 8.020
Gamma4 ($\widehat{\gamma_4}$)	—		—		−2.523 (0.546)	−3.593 to −1.453
Gamma5 ($\widehat{\gamma_5}$)	—		—		1.135 (0.604)	−0.048 to 2.318
Gamma6 ($\widehat{\gamma_6}$)	—		—		−0.201 (0.419)	−1.023 to 0.62
Gamma7 ($\widehat{\gamma_7}$)	—		—		0.015 (0.169)	−0.317 to 0.347
IPSS-R						
Low	Reference		Reference		Reference	
Intermediate ($\widehat{\beta_1}$)	1.358 (0.236)	0.894 to 1.821	0.521 (0.099)	0.327 to 0.715	−0.187 (0.159)	−0.500 to 0.125
High ($\widehat{\beta_2}$)	2.338 (0.241)	1.865 to 2.811	1.325 (0.108)	1.114 to 1.537	−0.243 (0.174)	−0.585 to 0.099
Very high ($\widehat{\beta_3}$)	1.937 (0.245)	1.458 to 2.417	2.041 (0.109)	1.827 to 2.255	0.736 (0.157)	0.428 to 1.044
Age, years ($\widehat{\beta_4}$)	0.027 (0.003)	0.02 to 0.034	0.048 (0.004)	0.04 to 0.056	0.009 (0.006)	−0.002 to 0.020
Interactions with time						
Gamma2 · intermediate ($\widehat{\beta_5}$)	0.006 (0.002)	0.003 to 0.010	—		—	
Gamma2 · high ($\widehat{\beta_6}$)	0.007 (0.002)	0.003 to 0.011	—		—	
Gamma2 · very high ($\widehat{\beta_7}$)	0.005 (0.002)	0.001 to 0.010	—		—	

	Transition[a]					
	5: Post-HSCT → Relapse		6: Post-HSCT → Dead		7:Relapse → Dead	
Parameter	Coef (SE)	95% CI	Coef (SE)	95% CI	Coef (SE)	95% CI
Baseline hazard						
Gamma0 ($\widehat{\gamma_0}$)	−8.906 (0.542)	−9.968 to −7.843	−9.057 (0.443)	−9.926 to −8.188	−7.209 (0.72)	−8.621 to −5.797
Gamma1 ($\widehat{\gamma_1}$)	1.385 (0.105)	1.179 to 1.592	1.256 (0.079)	1.101 to 1.412	1.16 (0.164)	0.838 to 1.482
Gamma2 ($\widehat{\gamma_2}$)	0.033 (0.004)	0.026 to 0.041	0.026 (0.002)	0.021 to 0.030	0.013 (0.005)	0.003 to 0.023

	Transition[a]					
	5: Post-HSCT → Relapse		6: Post-HSCT → Dead		7: Relapse → Dead	
Parameter	Coef (SE)	95% CI	Coef (SE)	95% CI	Coef (SE)	95% CI
IPSS-R						
Low	Reference		Reference		Reference	
Intermediate ($\widehat{\beta_1}$)	−0.014 (0.181)	−0.369 to 0.341	−0.143 (0.168)	−0.472 to 0.185	0.712 (0.31)	0.105 to 1.319
High ($\widehat{\beta_2}$)	0.129 (0.173)	−0.210 to 0.467	0.010 (0.161)	−0.307 to 0.326	0.277 (0.305)	−0.32 to 0.873
Very high ($\widehat{\beta_3}$)	0.335 (0.172)	−0.002 to 0.672	0.423 (0.155)	0.118 to 0.727	0.779 (0.297)	0.198 to 1.360
Age, years ($\widehat{\beta_4}$)	0.005 (0.004)	−0.003 to 0.013	0.026 (0.004)	0.017 to 0.034	0.008 (0.005)	−0.001 to 0.018
Time of entry in the state ($\widehat{\beta_8}$; 2 months difference)	−0.045 (0.001)	−0.062 to −0.028	0.005 (0.001)	0.001 to 0.010	—	

Abbreviations: HSCT, allogeneic hematopoietic stem-cell transplantation; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes.

[a]Transition 2 from MDS to post-HSCT is not included because of its deterministic nature (it is considered contingent upon the specific transplantation strategy scenario).

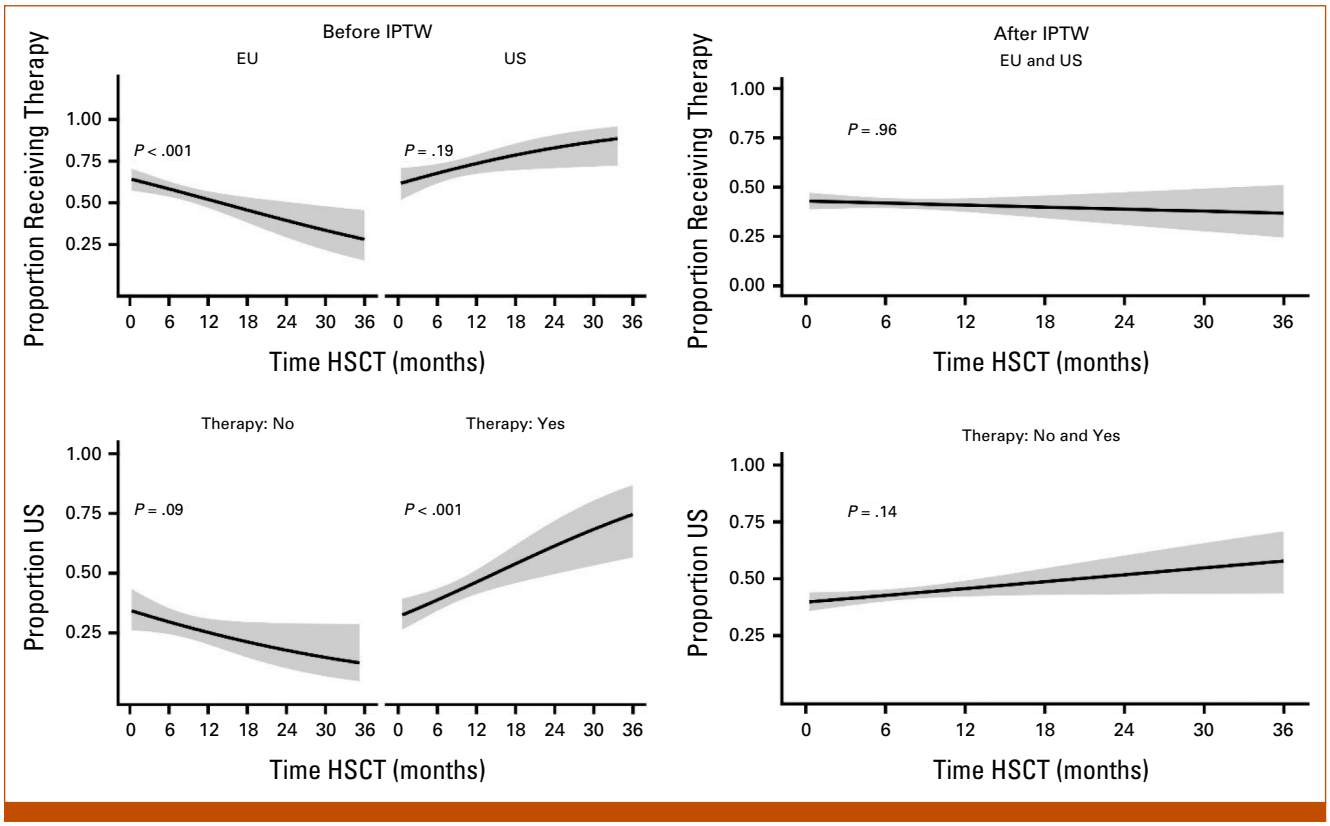

FIG 2. Balance assessment for disease-modifying therapy and EU/US group before and after IPTW. EU/US, Europe/United States; HSCT, allogeneic hematopoietic stem-cell transplantation; IPTW, inverse probability of treatment weighting.

corresponding estimate of the expected conditional QA-RMST, was obtained. To perform the decision analysis, the steps to follow were (1) reconstruct the continuous curve underlying the estimated discrete points, and (2) find its maximum. For this purpose, smoothing techniques through basis expansion (eg, natural cubic splines) were used.[25] Once the smoothed curves were obtained, for each of them, their global maximum $t^*_{x_1}$ within the closed interval $[t_1; t_2]$, that is, the point estimate of the optimum timing for the intervention, given the vector of covariates x_1, was found. Similarly, in the case of microsimulation with PSA, for each replication B: $b = 1, \ldots, B$, the maximum $t^{*(b)}_{x_1}$ of each of the replicated B curves was found. Finally, the optimal interval for HSCT for a specific combination of covariates x_1 at 95% confidence level was derived by considering the 2.5% and 97.25% percentiles of the distributions of the global maxima $\{t^{*(b)}_{x_1}\}_{b=1,\ldots,B}$. The R code is available online.[29]

RESULTS

Study Cohort

Overall, 7,118 patients from 26 institutions across Europe and the United States matched study inclusion criteria. Study participants included 4,397 men (62%) and 2,721 women (38%). Date range of diagnosis was from 2000 to 2018. Administrative end of follow-up was December 31, 2020. Patients were randomly stratified into a training cohort (n = 4,627, 65%) and a validation cohort (n = 2,491, 35%). According to the eligibility criteria of the target trial (Table 1), 3,854 and 2,075 patients, respectively, were included in the following analyses. Their characteristics are described in Appendix Table A1.

Disease Model

The observed transition frequencies are reported in Figure 1 and Appendix Figure A1. On the basis of data, the parameters associated with the transition hazards were estimated using the R package flexsurv,[26] except for transition 2, which was controlled by the intervention under consideration. Table 2 reports the estimated parameters of the transition-hazard functions of the selected multistate *disease model* (Appendix Table A2). In general, age and IPSS-R were risk factors for death (both) and disease-progression (IPSS-R). Moreover, the influence of covariates tended to diminish in subsequent transitions. This phenomenon can be attributed to the decreasing relevance of baseline characteristics once the disease status has changed. To adjust for possible unbalance because of disease-modifying therapy and EU/US group on the timing of HSCT, all post-HSCT transitions were adjusted through IPTW. Balance in confounders by comparing the therapy proportion in the EU/US group with respect to HSCT timing in transplanted patients, before and after weighing, was assessed using a logistic model (Fig 2). The relationship

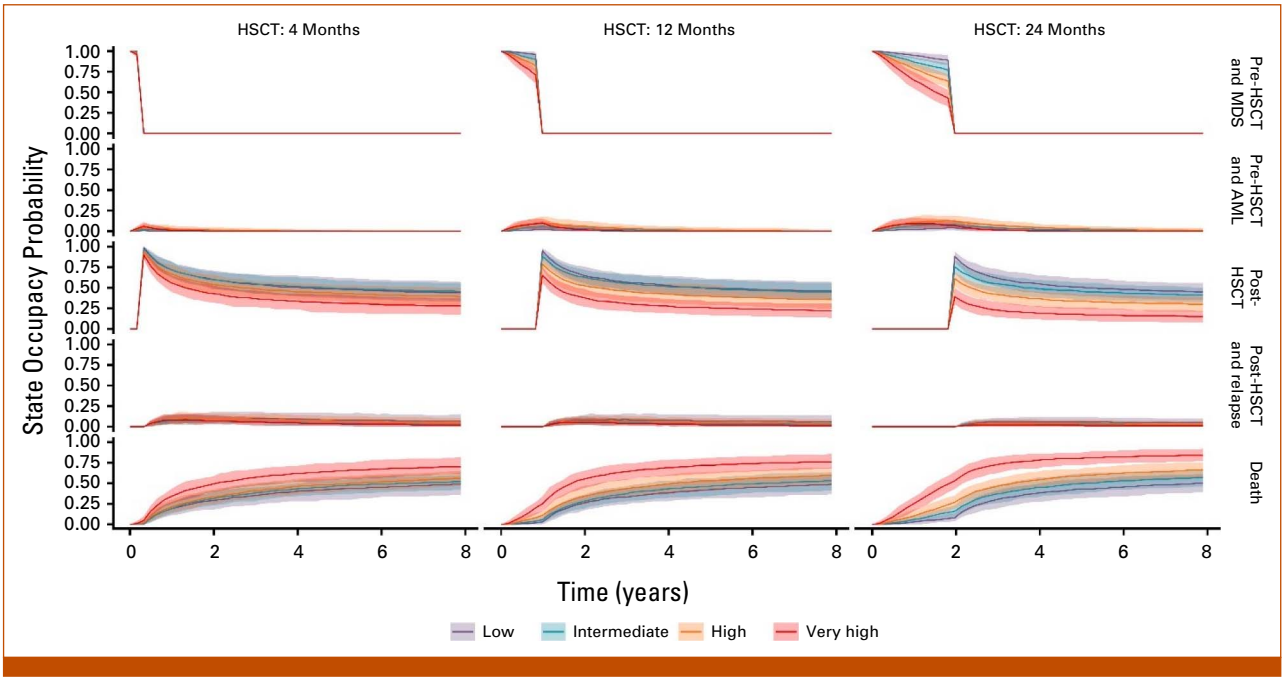

FIG 3. State occupancy probabilities (*y*-axis) over time (*x*-axis) obtained with the microsimulation with 95% CI from three possible scenarios corresponding to three different timings for HSCT (4, 12, and 24 months) according to IPSS-R; age is fixed at 60 years. The figure illustrates the decline in the probability of individuals being in the pre-HSCT and MDS state to zero at the specified time of HSCT. This is due to all subjects still alive who have not progressed to AML transitioning to the post-HSCT state. Consequently, there is a sudden increase in the probability of being post-HSCT from zero at the same time point. However, this probability does not reach one since some patients have already deceased or progressed to AML. Notably, the graph demonstrates the stratification of patient risk, particularly concerning the risk of death on the basis of different IPSS-R levels. HSCT, allogeneic hematopoietic stem-cell transplantation; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes.

between HSCT timing and confounders vanished in the weighted data set (right panel), unlike the original data set (left panel).

The models' overall goodness of fit for transition hazards was confirmed by comparing predicted values of the cause-specific cumulative hazard with nonparametric estimates (Appendix Figs A2 and A3) from both the training and the validation data sets.

Decision-Strategy Model Through Microsimulation

The microsimulation was performed using the R package *hesim*.[23] In the microsimulation, different scenarios of HSCT timing ranging from 1 to 36 months were performed. The time horizon *w* for the simulation was 8 years. A QALY value of 0.85 was assigned to the evolution to AML, whereas a QALY value of 0.90 was set to post-HSCT states. In each scenario, for each profile considering the different level of IPSS-R score and age values (40-70 years), $B = 200$ PSA replicates for a total of 80,000 patients were simulated. As an example, Figure 3 shows the state occupancy probabilities under three different policy scenarios corresponding to HSCT after 4, 12, and 24 months since MDS diagnosis for a 60-year-old individual with different levels of IPSS-R (purple: *low*; light blue: *intermediate*; orange: *high*; red: *very high*).

Decision-Strategy Analysis

For each patient profile, Figure 4 shows the estimated QA-RMST curves, which were smoothed using natural cubic splines with three internal knots (upper panel). By identifying the maximum of each QA-RMST smoothed curve, the optimal intervals of HSCT at 95% confidence level were derived (bottom panel).

DISCUSSION

This study assessed the challenge of identifying the optimal timing of a personalized intervention to maximize survival time, considering both pre- and post-intervention risks of death and adverse events in the setting of rare hematologic neoplasms with heterogeneous clinical course. An innovative methodologic approach with respect to previous works was developed.[22]

First, a decision-strategy model on the basis of microsimulations, a method increasingly applied in oncology to study clinical effectiveness and cost-effectiveness using observational data,[27] was used. This study demonstrated the relevance of decision-strategy models in the clinical context for optimizing treatment timing, as they allow to compare different treatment strategies. In addition, the use of microsimulation-based methods enabled to estimate mean

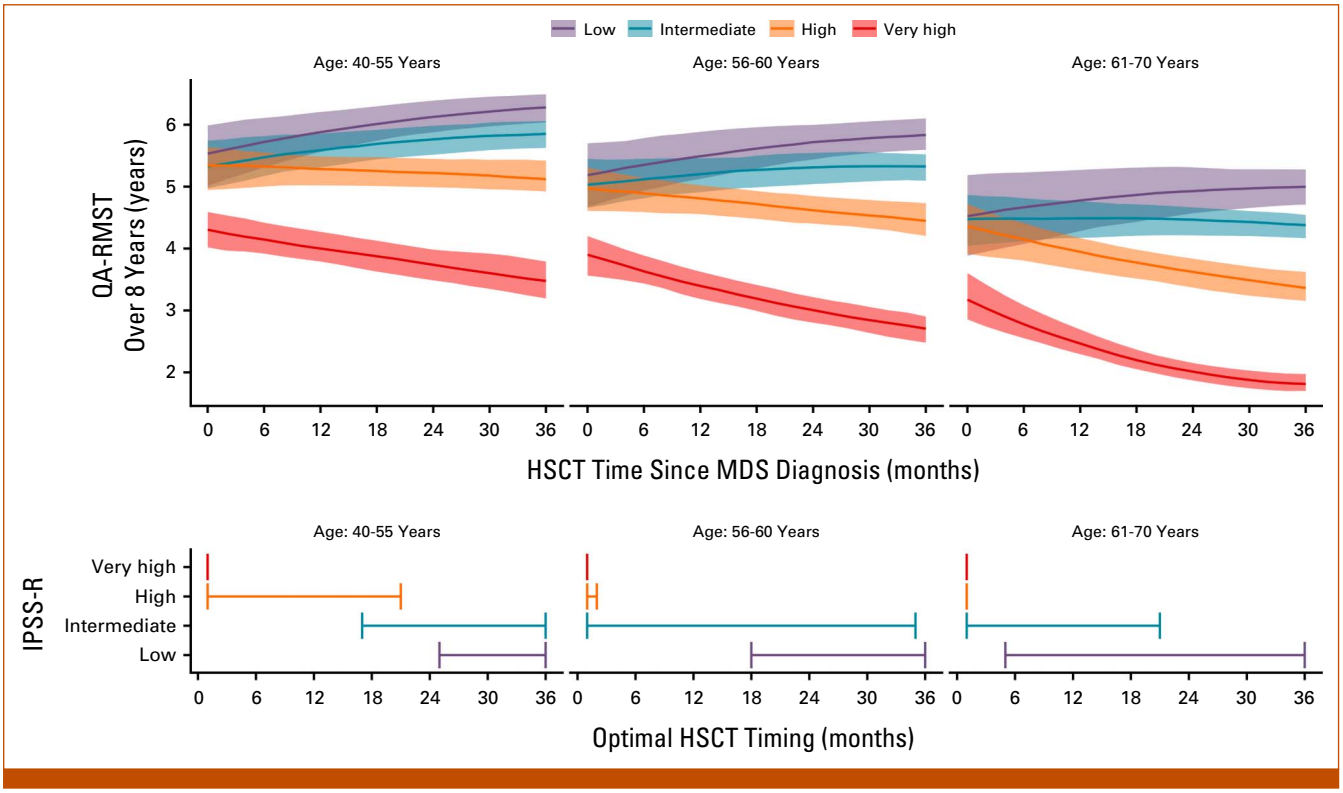

FIG 4. In the upper panel, the QA-RMST curves (*y*-axis) as function of HSCT timing (*x*-axis) and corresponding 95% CI obtained using the decision-strategy model according to patient profile. In the lower panel, the optimal windows for HSCT for each patient profile corresponding to time intervals for which the QA-RMST is maximum at 95% confidence level. It can be observed how, according to the IPSS-R, only lower-risk patients do not benefit from an early transplantation policy. HSCT, allogeneic hematopoietic stem-cell transplantation; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes; QA-RMST, quality-adjusted restricted mean survival time.

survival time conditioned on covariates from both Markov and semi-Markov models. This distinguishes the proposed approach from conventional models in the literature (eg, cohort models), as this novel decision-strategy model incorporates the treatment intervention as a state within the multistate model, providing a unique perspective on treatment optimization.

When developing a decision-strategy model, it is crucial to incorporate a realistic *disease model*. By including intermediate pre- and post-treatment states, the dynamic nature of the treatment-disease pathway was captured, achieving more accurate estimations of mean survival time. The semi-Markov property relaxed the restrictive Markov assumption and accounted for the dependence of individuals' transition risks between states on both the time since entering the state and the time of entry into the state. This is particularly relevant in describing the disease progression of chronic illnesses. Additionally, using spline-based parametric survival models allowed for the consideration of a flexible yet parametric shape for the transition hazards and for the inclusion of time-dependent effects of covariates as appropriate.

The proposed methodology places a strong emphasis on personalization, since it is in general capable to encompass factors such as demographics, clinical features, genomic information, risk of disease progression, and response to treatment. This enabled to identify the optimal timing of an intervention on a profile-specific level, recognizing that different individuals may benefit from different treatment timings. By incorporating this variability, the analysis accurately reflected the complexity of clinical decision making. In addition, a novel approach of emulating a target trial for optimizing the personalized timing of therapeutic intervention was introduced. By coupling a decision-modeling strategy with target trial emulation, a clear interpretation of the target quantity of interest, as well as transparency on the study design and intervention, was gained. This approach has not been previously explored in the context of transplantation for hematologic neoplasms.

Like any analysis on the basis of observational data, the obtained results rely on previously stated assumptions. Adjustment for disease-modifying therapy has been evaluated and balance with respect to the treatment timing has been achieved. However, it is important to recognize that unobserved confounding could still be present. To account for the uncertainty in parameter estimation using observed data, PSA was incorporated into the decision-strategy model, providing confidence intervals for the optimal timing of HSCT. Finally, validation is an important aspect of building a decision-strategy model.[28] Because of the lack of a

standardized practice within this framework, both internal validation and external validation of the disease model were conducted. Validating the microsimulation results directly proves challenging because of the absence of observed data on the specific intervention under study, which is essential for evaluating the decision-strategy model. From our perspective, the most suitable method to thoroughly validate the complete decision-strategy model would involve a comparison with the outcomes of a randomized clinical trial.

The developed methodology provided robust results in the context of a rare cancer with heterogeneous clinical and genomic background, and can be adapted and applied to different disease models.

In conclusion, the methodology developed in this article offers a structured framework to address a relevant clinical issue in the field of hematology. It makes valuable contributions: novel insights into how to develop decision models to identify the most favorable HSCT timing in a real-world context, and inform clinical decision making incorporating relevant individual patient information. This framework can be applied to provide medical insights for clinical issues that cannot be adequately addressed through randomized clinical trials.

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PRIOR PRESENTATION

Presented at the 43rd Annual Conference of the International Society of Clinical Biostatistics (ISCB), Newcastle, UK, August 21-25, 2022.

SUPPORT

Supported in part by European Union - Horizon 2020/2023 program (GenoMed4All project #101017549 to M.G.D.P.; U.P.; M.D-C.; P.F.; T.H.; Synthema project, #1101095530 to M.G.D.P.); European Union - Next Generation EU - NRRP M6C2 (Investment 2.1 Enhancement and strengthening of biomedical research in the NHS – Project PNRR-MAD-2022-12376695 to M.G.D.P.); AIRC Foundation (Associazione Italiana per la Ricerca contro il Cancro, Milan Italy – Project #22053 and # 29483 to M.G.D.P); 5×1000 MYNERVA (Myeloid Neoplasms Research Venture AIRC - project #21267 to M.G.D.P); PRIN 2017 (Ministry of University & Research, Italy – Project 20229B28PE and Project 2017WXR7ZT to M.G.D.P.).

DATA SHARING STATEMENT

Requests for access to data from the study should be addressed to GenoMed4All/Synthema Scientific committee (please contact Matteo G Della Porta at matteo.della_porta@hunimed.eu). All proposals requesting data access will need to specify how the data will be used, and all proposals will need the approval of the GenoMed4All/Synthema scientific committee before data release.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Research Funding: Amgen (Inst), Janssen (Inst), Novartis (Inst), BerGenBio (Inst), Celgene (Inst), Curis (Inst)
Patents, Royalties, Other Intellectual Property: Part of a patent for a TFR-2 antibody (Rauner et al. Nature Metabolics 2019)
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Research Funding: Bristol Myers Squibb/Celgene (Inst)
Travel, Accommodations, Expenses: Jazz Pharmaceuticals, Bristol Myers Squibb, Pharmaessentia

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

The present research is part of the activities of Dipartimento di Eccellenza 2023-2027 of the Department of Mathematics, Politecnico di Milano.

REFERENCES

1. McNeil BJ, Pauker SG: Decision analysis for public health: Principles and illustrations. Annu Rev Public Health 5:135-161, 1984
2. Pauker SG, Kassirer JP: Decision analysis. N Engl J Med 316:250-258, 1987
3. Frazão TDC, Camilo DGG, Cabral ELS, et al: Multicriteria decision analysis (MCDA) in health care: A systematic review of the main characteristics and methodological steps. BMC Med Inform Decis Mak 18:90, 2018
4. Subbiah V: The next generation of evidence-based medicine. Nat Med 29:49-58, 2023
5. Swerdlow SH, Campo E, Pileri SA, et al: The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127:2375-2390, 2016
6. Cazzola M, Della Porta MG, Malcovati L: The genetic basis of myelodysplasia and its clinical relevance. Blood 122:4021-4034, 2013
7. Greenberg PL, Tuechler H, Schanz J, et al: Revised International Prognostic Scoring System for myelodysplastic syndromes. Blood 120:2454-2465, 2012
8. Bernard E, Tuechler H, Greenberg PL, et al: Molecular international prognostic scoring system for myelodysplastic syndromes. NEJM Evid 1:1-14, 2022
9. Malcovati L, Hellström-Lindberg E, Bowen D, et al: Diagnosis and treatment of primary myelodysplastic syndromes in adults: Recommendations from the European LeukemiaNet. Blood 122: 2943-2964, 2013
10. de Witte T, Bowen D, Robin M, et al: Allogeneic hematopoietic stem cell transplantation for MDS and CMML: Recommendations from an international expert panel. Blood 129:1753-1762, 2017
11. Della Porta MG, Gallì A, Bacigalupo A, et al: Clinical effects of driver somatic mutations on the outcomes of patients with myelodysplastic syndromes treated with allogeneic hematopoietic stem-cell transplantation. J Clin Oncol 34:3627-3637, 2016
12. Hernán MA, Sauer BC, Hernández-Díaz S, et al: Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol 79:70-75, 2016
13. Rutter CM, Zaslavsky AM, Feuer EJ: Dynamic microsimulation models for health outcomes: A review. Med Decis Making 31:10-18, 2011
14. Tentori CA, Gregorio C, Robin M, et al: Clinical and genomic-based decision support System to define the optimal timing of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic syndromes (MDS). Blood 142:197, 2023
15. GenoMed4All - Genomics For Next Generation Healthcare. www.genomed4all.eu
16. Synthema – Synthetic Haematological Data. www.synthema.eu
17. ERN-EuroBloodNet, the European Reference Network on Rare Hematological Diseases | EuroBloodNet. www.eurobloodnet.eu
18. Hernán MA: Methods of public health research—Strengthening causal inference from observational data. N Engl J Med 385:1345-1348, 2021
19. Hernan MA, Robins JM: Causal Inference: What If. Boca Raton, FL, CRC Press, 2021
20. Putter H, Fiocco M, Geskus RB: Tutorial in biostatistics: Competing risks and multi-state models. Stat Med 26:2389-2430, 2007
21. Royston P, Parmar MKB: Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med 21:2175-2197, 2002
22. Nane GF, van Geloven N, le Cessie S, et al: Causal inference with multi-state models, applied on estimating the effect of the IUI treatment timing for couples with unexplained subfertility. http://resolver.tudelft.nl/uuid:37e09c1e-68fa-4419-b0f5-682b41e1f253
23. Incerti D, Jansen JP: hesim: Health economic simulation modeling and decision analysis, 2021. arXiv:2102.09437
24. O'Hagan A, Stevenson M, Madan J: Monte Carlo probabilistic sensitivity analysis for patient level simulation models: Efficient estimation of mean and variance using ANOVA. Health Econ 16: 1009-1023, 2007
25. Ramsay JO, Silverman BW: Functional Data Analysis. New York, NY, Springer, 2005
26. Jackson CH: flexsurv: A platform for parametric survival modeling in R. J Stat Softw 70:i08, 2016
27. Çağlayan Ç, Terawaki H, Chen Q, et al: Microsimulation modeling in oncology. JCO Clin Cancer Informatics 10.1200/CCI.17.00029
28. Caro JJ, Briggs AH, Siebert U, et al: Modeling good research practices—Overview: A report of the ISPOR-SMDM modeling good research practices task force-1. Value Health 15:796-803, 2012
29. OptTimeHSCT. https://github.com/caterinagregorio/OptTimeHSCT

APPENDIX 1. SUPPLEMENTARY MATERIAL

Causal Assumptions

To identify the causal contrasts involving the potential outcome $D^{(g)}$, the main assumptions for causal inference (ie, consistency, conditional exchangeability, and positivity) must hold.[7] In our context, *consistency* refers to the principle that the time to the terminal event in a world where we intervene with strategy g leading the time of the treatment to be fixed at a specific value t is the same as the survival in the real world where we observe a time to treatment equal to t. *Conditional exchangeability* assumes that the potential outcome is independent of the observed timing of the treatment, conditionally on the observed vector of covariates X. Methods to adjust for covariates contained in the vector X but not on the conditioning vector X_1, denoted with $X_2 = X - X_1$, are explained later. Moreover, censoring times are assumed to be conditionally independent of all potential event times. Finally, to satisfy *positivity*, for each vector of covariates X, the probability of receiving the intervention for each $g = t$ is positive (ie, all individuals included are eligible to receive the treatment at each time $t \in [t_1; t_2]$).

Definition of Inverse Probability of Treatment Weighting

For each individual with vector x_2 of observed confounders, the propensity score[11,12] in our setting is defined as

$$ps = \Pr(T = t \mid D > t, A > t, X_2 = x_2),$$

where T the time of the allogeneic hematopoietic stem-cell transplantation (HSCT), A the time to AML, and D the time to death. Specifically, X_2 is the vector of covariates for pre-HSCT transition (ie, contained in the vector X but not on the conditioning vector X_1): the disease-modifying therapy (*yes* or *no*) status and the consortium-group (EU or US).

The stabilized weights by inverse probability of treatment weighting are proportional to the inverse of the propensity score ps and can then be obtained as

$$sw = \frac{\Pr(T = t \mid D > t, A > t)}{\Pr(T = t \mid D > t, A > t, X_2 = x_2)}.$$

Both numerator and denominator in sw are estimated fitting flexible parametric transition hazards coupled with Aalen-Johansen estimator for the transition probability in a competing-risk/multistate framework.

Disease Model Formulas

According to the Royson-Parmar model, the logarithm of each transition j cumulative hazard is specified as

$$\log(H_j(t)) = \text{gammao} + \sum_{k=1}^{K+1} \text{gammak}\, b_k(t),$$

where K are the number of internal knots, and $b_k(t)$ is the k^{th} basis of the natural cubic spline,

$$\text{gammao} = \begin{cases} \gamma_0 + \beta_1 \times \text{intermediate} + \beta_2 \times \text{high} + \beta_3 \times \text{very high} \\ \quad + \beta_4 \times \text{age if } j = 1, 3, 4, 7 \\ \gamma_0 + \beta_1 \times \text{intermediate} + \beta_2 \times \text{high} + \beta_3 \times \text{very high} + \beta_4 \\ \quad \times \text{age} + \beta_8 \times \text{time of entry in the state if } j = 5, 6 \end{cases}$$

$$\text{gammak} = \begin{cases} \gamma_k + \beta_5 \times \text{intermediate} + \beta_6 \times \text{high} + \beta_7 \times \text{very high} \\ \text{for } j = 1 \text{ and } k = 2 \\ \gamma_k \text{ in all other cases} \end{cases}.$$

Microsimulation Algorithm

Formally, simulating the path of an individual in a given multistate model means finding the J distinct jumps between health states. Here, t_j denotes the time of a generic jump j. Below is reported one step of the microsimulation algorithm for a subject i with covariate vector x_{1i} and assigned to a treatment strategy $g = t$.

1. Let r be the state entered at time t_j. The number of permitted stochastic transitions from state r is given by n_r.
2. If $t_j = t$ and the individual is still in the state pre-HSCT and myelodysplastic syndromes (MDS), then the next state s is post-HSCT.
3. Else simulate a time for each of the n_r permitted transitions and set the time of the transition t_{j+1} equal to the minimum simulated time and set the next state s to the corresponding state.
4. Set $r = s$ and $t_j = t_{j+1}$. If the individual is not in the death state and $t_j \leq w$, repeat the previous steps.

Inclusion Criteria for the Study Cohort

Inclusion criteria were age 18 years and older, a diagnosis of primary MDS according to WHO 2016-2017 criteria and available information on Revised International Prognostic Scoring System–related variables collected at diagnosis for patients who did not receive HSCT, before HSCT for patients who were transplanted upfront, and before starting disease-modifying treatments for patients who underwent pre-HSCT cytoreduction. Patients affected with therapy-related MDS, AML from MDS, or with incomplete information on IPSS-M variables were excluded. Patients were reclassified according to WHO 2022 and International Consensus Classification of Myeloid Neoplasms (ICC) criteria.

TABLE A1. Descriptive Statistics of Training and Validation Cohorts

Characteristic	Main (n = 3,854)	Validation (n = 2,075)
Age, years, median (IQR)	69 (61-77)	69 (60-76)
Sex, No. (%)		
Female	1,471 (38)	807 (39)
Male	2,383 (62)	1,268 (61)
IPSS-R, No. (%)		
Low	1,453 (38)	783 (38)
Intermediate	949 (25)	496 (24)
High	740 (19)	401 (19)
Very high	712 (18)	395 (19)
IPSS-M, No. (%)		
Low	1,115 (29)	589 (28)
Moderate low	552 (14)	301 (15)
Moderate high	524 (14)	262 (13)
High	764 (20)	435 (21)
Very high	899 (23)	488 (24)
Disease-modifying therapy, No. (%)	1,786 (46)	979 (47)
Consortium group, No. (%)		
EU	2,468 (64)	1,314 (63)
US	1,386 (36)	761 (37)

Abbreviations: EU, Europe; IPSS-R, Revised International Prognostic Scoring System; IPSS-M, Molecular-International Prognostic Scoring System; US, United States.

TABLE A2. Results of the Transition Hazards Models Used to Estimate the IPTW

	Transition					
	1: MDS → AML		2: MDS → Post-HSCT		3: MDS → Dead	
Parameter	Coef (SE)	95% CI	Coef (SE)	95% CI	Coef (SE)	95% CI
Denominator						
Baseline hazard						
Gamma0 ($\widehat{\gamma_0}$)	−11.032 (0.512)	−12.035 to −10.028	−10.021 (0.803)	−11.595 to −8.447	−12.325 (0.661)	−13.621 to −11.029
Gamma1 ($\widehat{\gamma_1}$)	1.713 (0.119)	1.479 to 1.947	1.376 (0.237)	0.911 to 1.84	1.652 (0.126)	1.404 to 1.899
Gamma2 ($\widehat{\gamma_2}$)	0.022 (0.003)	0.016 to 0.028	−0.093 (0.057)	−0.204 to 0.018	0.024 (0.006)	0.012 to 0.035
Gamma3 ($\widehat{\gamma_3}$)	—		0.178 (0.105)	−0.028 to 0.385		
Gamma4 ($\widehat{\gamma_4}$)	—		−0.073 (0.062)	−0.194 to 0.047		
Disease-modifying therapy						
No	Reference		Reference		Reference	
Yes ($\widehat{\beta_1}$)	1.067 (0.085)	0.901 to 1.233	1.067 (0.085)	0.901 to 1.233	0.365 (0.123)	0.124 to 0.605
Group/continent						
EU	Reference		Reference		Reference	
US ($\widehat{\beta_2}$)	−1.943 (0.321)	−2.573 to −1.313	−1.946 (0.322)	−2.577 to −1.315	0.674 (0.115)	0.449 to 0.899
Interaction						
Yes · US ($\widehat{\beta_3}$)	1.522 (0.332)	0.871 to 2.173	1.526 (0.333)	0.874 to 2.178	−0.187 (0.166)	−0.512 to 0.139

	Transition					
	1: MDS → AML		2: MDS → Post-HSCT		3: MDS → Dead	
Parameter	Coef (SE)	95% CI	Coef (SE)	95% CI	Coef (SE)	95% CI
Numerator						
Baseline hazard						
Gamma0 ($\widehat{\gamma_0}$)	−10.648 (0.500)	−11.627 to −9.668	−12.766 (1.357)	−15.426 to −10.105	−11.752 (0.652)	−13.03 to −10.474
Gamma1 ($\widehat{\gamma_1}$)	1.74 (0.117)	1.512 to 1.969	2.037 (0.346)	1.359 to 2.714	1.623 (0.125)	1.377 to 1.868
Gamma2 ($\widehat{\gamma_2}$)	0.024 (0.003)	0.018 to 0.030	−1.355 (0.199)	−1.746 to −0.965	0.023 (0.006)	0.011 to 0.034
Gamma3 ($\widehat{\gamma_3}$)	—		2.356 (0.275)	1.818 to 2.895	—	
Gamma4 ($\widehat{\gamma_4}$)	—		−0.997 (0.097)	−1.188 to −0.807	—	

Abbreviations: HSCT, allogeneic hematopoietic stem-cell transplantation; IPTW, inverse probability of treatment weighting; MDS, myelodysplastic syndromes.

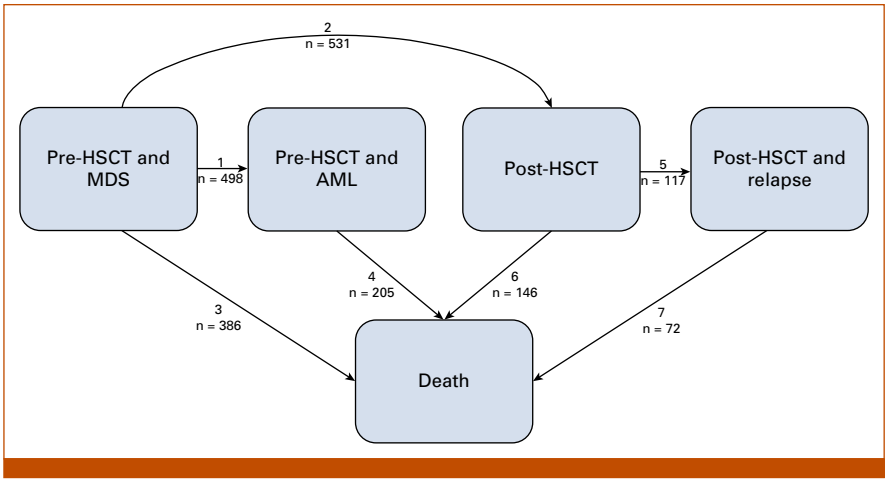

FIG A1. Multistate model structure and observed number of transitions in the validation cohort. HSCT, allogeneic hematopoietic stem-cell transplantation; MDS, myelodysplastic syndromes.

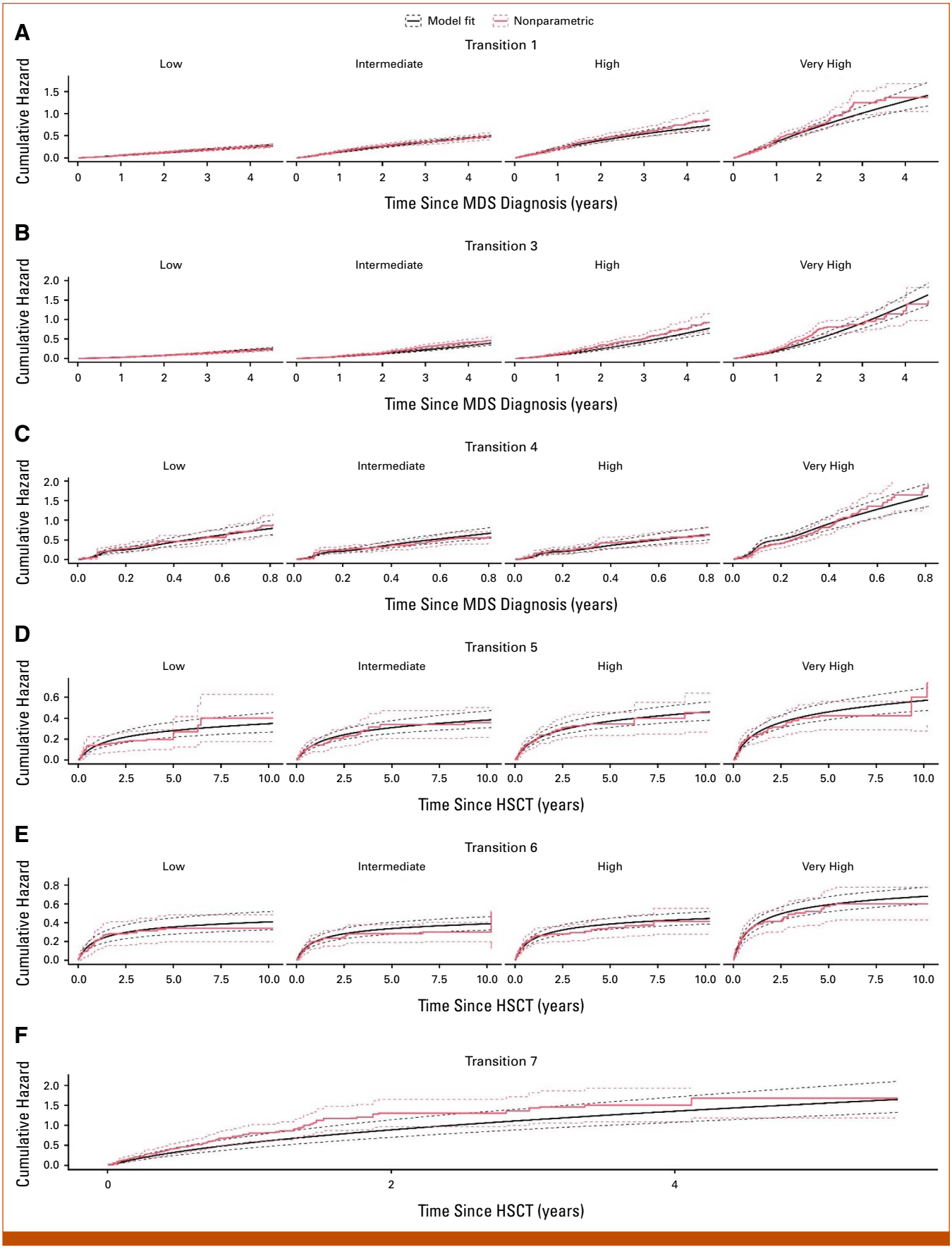

FIG A2. Goodness of fit of transition hazard models on the *main* cohort: (A) transition 1, (B) transition 3, (C) transition 4, (D) transition 5, (E) transition 6, and (F) transition 7. For each transition, predicted cumulative transition hazards obtained from the (continued on following page)

FIG A2. (Continued). spline-based parametric cause-specific models estimated on the *main* data set (black curves) have been compared with the nonparametric estimates obtained from the same data set according to IPSS-R values (red curves); age was considered fixed at the mean value of patients at risk for the transition. Dashed lines correspond to 95% CI. To prevent unstable nonparametric estimates, the *x*-axis limit for each transition was specifically determined to maintain a minimum of 10 patients at risk throughout time, while considering the IPSS-R strata. All transition hazard models show a satisfactory goodness of fit since the 95% CI of the model fit overlaps the corresponding nonparametric estimate. HSCT, allogeneic hematopoietic stem-cell transplantation; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes.

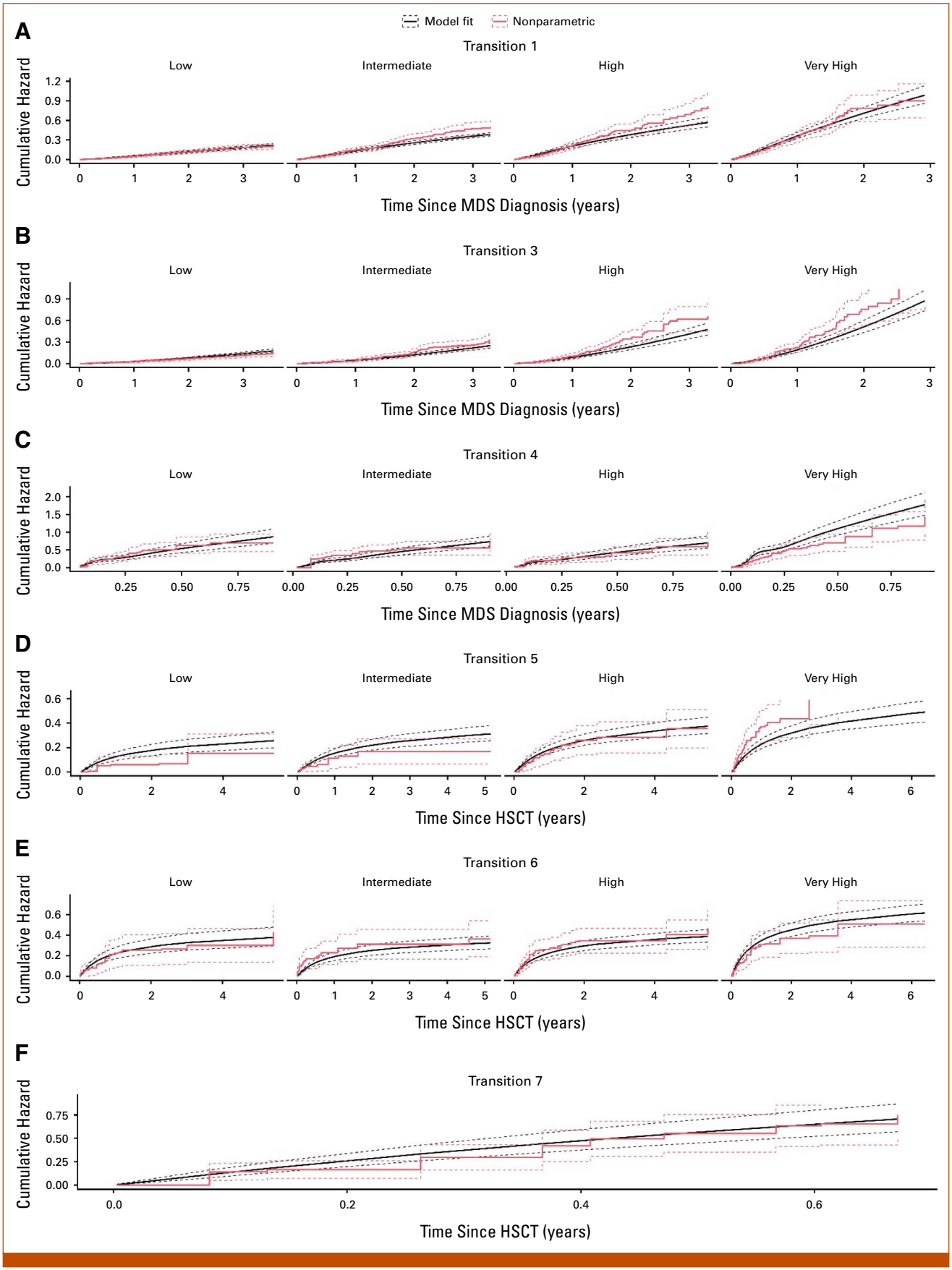

FIG A3. Out-of-sample goodness-of-fit of transition hazard models on the validation cohort: (A) transition 1, (B) transition 3, (C) transition 4, (D) transition 5, (E) transition 6, and (F) transition 7. For each transition, predicted cumulative transition (continued on following page)

FIG A3. (Continued). hazards obtained from the spline-based parametric cause-specific models estimated on the *main* data set (black curves) have been compared with the nonparametric estimates obtained from the *test* data set according to IPSS-R values (red curves); age was considered fixed at the mean value of patients at risk for the transition. Dashed lines correspond to 95% CI. To prevent unstable nonparametric estimates, the *x*-axis limit for each transition was specifically determined to maintain a minimum of 10 patients at risk throughout time, while considering the IPSS-R strata. All transition hazard models show a satisfactory goodness of fit since the 95% CI of the model fit overlaps the corresponding nonparametric estimate. HSCT, allogeneic hematopoietic stem-cell transplantation; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes.