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A post-transplant optimized transplant-specific risk score in myelodysplastic syndromes

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Allogeneic hematopoietic stem-cell transplantation (HSCT) remains the only potentially curative therapy for myelodysplastic syndromes (MDS), but treatment risks include relapse and non-relapse mortality (NRM). Whereas relapse following HSCT is typically dictated by disease-related factors, NRM is more influenced by patient- (performance status, co-morbidity, etc.) and transplant-related factors (donor type, conditioning intensity, graft-*versus*-host disease prophylaxis regimen, etc.). In order to improve transplant decision-making for the individual MDS patient, better prediction of HSCT outcomes, by including both relapse and NRM predictors in a comprehensive individualized and dynamic risk model, would be optimal. So where do we stand currently?

The prognosis of MDS has historically been based on the International Prognostic Scoring System (IPSS). For transplant decision-making, Markov models based on the IPSS have documented that MDS patients with low- and intermediate-1-risk MDS have better survival outcomes without transplant, whereas transplantation results in better survival outcomes for patients with intermediate-2- and high-risk MDS.[1,2] The Revised International Prognostic Scoring System (R-IPSS), a refinement of the IPSS, is used to prognosticate MDS at diagnosis, particularly the risk for transformation to acute myeloid leukemia,[3] and is often used as part of the decision to proceed to transplantation or not.[4]

While the IPSS and R-IPSS focus on disease features, they do not consider patient- and transplant related factors relevant to HSCT outcome. Attempts have, therefore, been made to develop MDS transplant-specific risk scores to predict survival better. These scores include the transplantation risk index developed by the *Gruppo Italiano Trapianto di Midollo Osseo* (GITMO)[4] registry using 519 patients as well as a risk score from the Center for International Blood and Marrow Transplant Research (CIBMTR)[5], using 1,519 patients. Both of these indices identified similar prognostic variables (including the R-IPSS), dividing MDS transplant recipients into four risk groups with overall survival rates ranging from 5-76%. However, these indices have not been universally adopted in current practice. While the GITMO index has not been externally validated, the CIBMTR index was validated on a distinct subset of patients from within the CIBMTR database. Gagelmann *et al.* now report on another composite risk score with better predictive ability than the existing indices.[6]

The authors compiled a cohort of 1,059 adult patients (≥18 years) with MDS from the European Society for Blood and Marrow Transplantation (EBMT) registry who underwent HLA-matched HSCT from a related or unrelated donor between 2000 to 2014. Using a Cox proportional hazards model they identified seven variables with significant impact on overall survival: age >50 years, matched unrelated donor, Karnofsky Performance Status <90%, very poor cytogenetics or monosomal karyotype, positive cytomegalovirus status of the recipient, peripheral blood blasts >1% and platelet count ≤50 x 10^9/L. Of these, age and cytogenetic risk were the strongest predictors of survival, based on hazard ratios for death, and given more weight than the other factors in the final score. Four prognostic groups were identified (low, intermediate, high and very-high risk) with overall survival rates of 68.7%, 43.2%, 26.6% and 9.5%, respectively.

How does the EBMT score described in the paper by Gagelmann *et al.* compare to the prior CIBMTR and GITMO scores as well as the R-IPSS itself? One approach would be to compare the concordance or c-statistic (measured as area under the receiver operating curve) of the different indices. The c-statistic is used to compare the goodness of fit of logistic regression models with values that range from 0.5 to 1.0. A c-statistic of 0.5 indicates the predictive ability of the index is no better than chance while a c-statistic in the 0.7-0.8 range has reasonable discriminatory power. Looking at the c-statistic following cross- validation, the EBMT transplant risk index scored 0.609 (95% confidence interval: 0.588 to 0.629), which was better than the CIBMTR (0.555) and GITMO (0.579)

indices as well as the R-IPSS (0.551). The authors concluded that the EBMT risk index is a better composite prognostic tool for MDS transplantation outcomes than existing indices, albeit acknowledging that the benefit is modest. However, we have caveats. In general, the c-statistic for an index would be expected to decrease slightly when applied to an external validation dataset (in comparison to the parent dataset from which it was derived) and this must be considered when comparing c-statistics for the externally validated GITMO and CIBMTR indices to the non-externally validated EBMT risk index. Validation of the EBMT risk index in an independent cohort of patients would provide a better estimate of its discriminatory power. Furthermore, as the authors acknowledge, the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI), a well validated and widely used tool to predict NRM,[7] was not part of the variables examined (due to insufficient data) and the EBMT predictive model would be expected to improve if the HCT-CI had been incorporated.

Although the above indices incorporate information on MDS karyotype, they lack MDS genomic data, which are increasingly important for predicting relapse and, to an extent NRM, after transplantation. A large analysis using the CIBMTR database (n=1,514) examined the association between pre-transplant mutational profile and post-

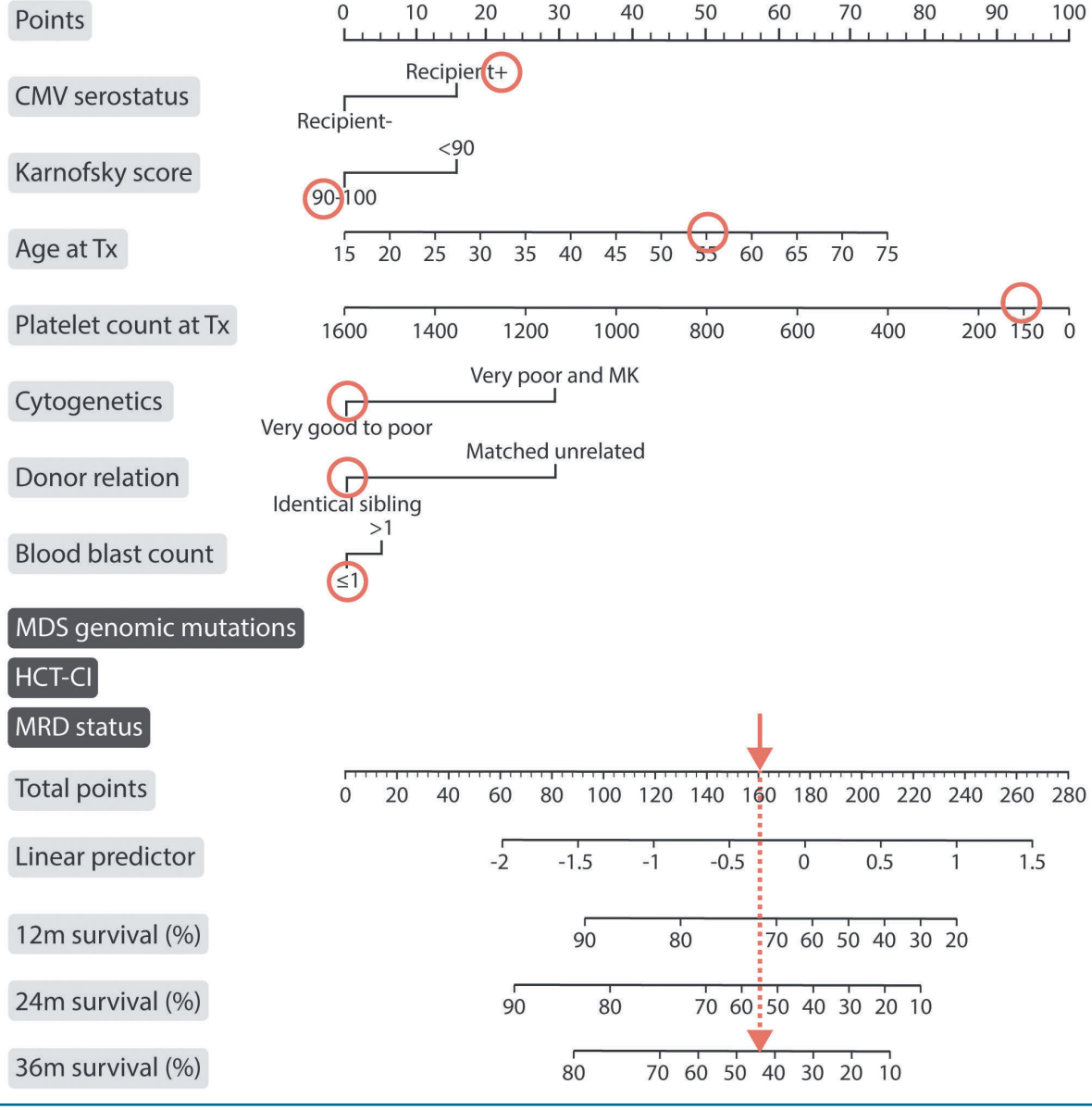

Figure 1. Nomogram adapted from Gagelmann *et al.*[8] showing an example calculation. In this example a 55-year old, cytomegalovirus (CMV)-positive patient with a Karnofsky performance status of 90, platelet count of 150x10^9/L, very good cytogenetics, <1% blasts and a matched sibling donor would get 160 points with a 2-year survival in the 50-60% range. The c-statistic for the EBMT index was 0.609 (95% confidence interval: 0.588 t0 0.629. We also highlight factors not included in the original nomogram – myelodysplastic syndrome (MDS) mutations, minimal residual disease (MRD) and Hematopoietic Cell Transplantation Comobidity Index (HCT-CI) – which could enhance the discriminatory power of the index.

transplant outcomes using targeted mutational analysis with a next-generation sequencing panel. In this cohort, *TP53* and *RAS* pathway mutations were strongly associated with poorer overall survival and earlier relapse independently of transplant conditioning intensity. There was also an indication that patients with *JAK2* mutations had increased NRM after ablative conditioning transplants.[7] In this context, there has been an attempt to include genomic data into the GITMO index.[8] In a cohort of 401 patients, using massively parallel sequencing for mutational analysis, *TP53* mutations were again identified as adverse prognostic markers. In addition, spliceosome mutations signifying a secondary-type acute myeloid leukemia phenotype, *ASXL1* and *RUNX1* were also associated with poorer outcomes. With MDS mutational analysis becoming routine practice in the clinic, it is important that future iterations of transplant risk models incorporate MDS genomic data.

The impact of disease persistence as measurable residual disease – variably measured by multi-parameter flow cytometry, cytogenetics/fluorescence *in situ* hybridization, and increasingly by next-generation sequencing – has been of great interest as an independent dynamic predictor of relapse. In MDS, the presence of measurable residual disease in the early post-transplant period (assessed by multi-parameter flow cytometry or cytogenetics/fluorescence *in situ* hybridization) is associated with significantly poorer outcomes.[9] Further studies are needed to better define the impact of pre- and post-transplant measurable residual disease, but we expect this to be an important and dynamic predictor for individualized MDS transplant risk prediction in the future.

With regards to individualized risk prediction, the authors of the current study define a user-friendly nomogram for scoring the various elements of the index in finer detail and with greater prognostic power (c-statistic 0.609) (Figure 1). In Figure 1 we have in addition highlighted three missing variables that would likely add to the discriminatory power of this index (i.e. pre-transplant mutational/genomic analysis, HCT-CI and minimal residual disease status).

We also note that for poor-risk cohorts, failure after transplantation includes both NRM and relapse at equivalent frequency (~40%). This offers opportunities for progress, especially for reducing NRM failures. For instance, cytomegalovirus serostatus of the recipient and its impact on post-transplant survival and immune reconstitution has been an area of increasing research.[10] In this study there was a moderately high risk of cytomegalovirus reactivation (39%) with significant impairment of overall survival.[6] As the authors point out, optimizing the use of antiviral agents active against cytomegalovirus, such as letermovir, which have been shown to be useful in high-risk settings,[11] may improve NRM in a lower-risk HLA-matched cohort. Similarly, avoiding ablative conditioning in *TP53*- and *JAK2*-mutant MDS, in which it offers no benefit and may even be deleterious, may further reduce NRM after transplantation, while ablative conditioning may improve outcomes of *RAS* pathway-mutant MDS.[8] In the future, studies of preemptive immunomodulation strategies (e.g. tumor vaccines, donor lymphocyte infusions) based on individual dynamic risk scoring before and after transplantation may be considered.

In summary, Gagelmann *et al.* present a new composite risk index to predict MDS transplant survival outcomes which incorporates both disease- and patient-related factors. They document a moderate improvement of predictive power compared to existing indices. A useful nomogram is provided as a step towards individualized outcome prediction. External validation in an independent dataset, and the future incorporation of the HCT CI, MDS genomic data and minimal residual disease status will be important next steps toward the goal of individualized, dynamic MDS transplant outcome prediction and treatment decision-making.

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