

# Methodological Concerns Regarding the Validation of the CHARM Score for Cord Blood Transplantation

## Kord Kanı Transplantasyonu için CHARM Skorunun Validasyonuna İlişkin Metodolojik Endişeler

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### To the Editor,

We read with great interest the recent study by Kato et al. [1]. They conducted a retrospective validation of the Composite Health Risk Assessment Model (CHARM) score in 321 adults undergoing cord blood transplantation (CBT) and demonstrated its utility in predicting overall survival and relapse, but not non-relapse mortality (NRM). While this study provides valuable insights into risk stratification for CBT, we have methodological concerns regarding the multivariate analysis, particularly for NRM, that may affect the validity of the results.

First, established statistical guidelines recommend approximately 10 events per variable (EPVs) to ensure reliability in multivariable regression models [2,3,4,5]. In the study by Kato et al. [1], the multivariate analysis for NRM included seven variables (CHARM score, age, sex, refined Disease Risk Index, conditioning regimen, cord blood total nucleated cell count, and HLA mismatches), as shown in Table 2 of the original article. However, the cumulative incidence of NRM at 2 years was 9.1% in the lower CHARM group (n=223) and 15.5% in the higher group (n=98), yielding an estimated total of approximately 35 NRM events, with 20.3 events in the lower group and 15.2 in the higher group. With only 35 events for 7 variables, the EPV value is roughly 5, which falls below the recommended threshold of 10 EPVs [2,3,4,5]. This suggests a risk of overfitting, potentially leading to unreliable hazard ratio estimates for NRM, as evidenced by the non-significant result (hazard ratio: 1.17, 95% confidence interval: 0.68-1.99, p=0.560).

Second, although the study reported univariate analyses before multivariate modeling, the variable selection process for inclusion in the multivariate model was not explicitly described. Guidelines emphasize that variables should be selected based on clinical relevance or univariate significance to avoid overfitting [6].

The authors adjusted for all covariates without clear justification, which could have introduced bias. For instance, the non-significant association between CHARM score and NRM in multivariate analysis might have been influenced by the limited events relative to the number of variables. We recommend that the authors consider sensitivity analyses, such as reducing the number of variables in the NRM model or using penalized regression techniques, to validate their findings. Additionally, reporting the exact number of events for each endpoint would enhance transparency.

Despite these concerns, the study remains impactful for highlighting the role of the CHARM score in CBT. Future prospective studies with larger cohorts are needed to confirm these results.

**Keywords:** Prediction, Cord blood transplantation, Methodological concerns

**Anahtar Sözcükler:** Prediksiyon, Kord kanı transplantasyonu, Metodolojik endişeler

### Ethics

**Informed Consent:** Not applicable.

### Footnotes

### Authorship Contributions

Concept: J.L.; Design: J.L.; Writing: Y.Y., J.L.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

## References

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## Reply from the Authors:

We appreciate these thoughtful comments from Yang and Liu regarding our recent study validating the Composite Health Risk Assessment Model (CHARM) score in adults undergoing single-unit unrelated cord blood transplantation (CBT). Their remarks highlight important methodological considerations, particularly related to the multivariable analysis for non-relapse mortality (NRM).

In our study [1], adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the CHARM score were estimated using multivariable models that incorporated all clinically relevant covariates, including age, recipient sex, refined disease risk index score, conditioning regimen, cryopreserved cord blood total nucleated cell count, and HLA disparities. Our results showed that the CHARM score did not predict NRM in adults undergoing unrelated single-unit CBT, differing from findings in the original CHARM report [2].

First, we agree with Yang and Liu's observation that the number of NRM events was limited. Indeed, 56 NRM events occurred, resulting in an events-per-variable ratio below the

commonly recommended threshold of 10. We acknowledge that this limitation may have contributed to the non-significant association between the CHARM score and NRM in our multivariable analysis.

Second, with respect to variable selection, all covariates included in the primary multivariable model were chosen based on established clinical relevance in CBT, which may also have influenced the observed lack of significance. To address the potential for overfitting, we conducted sensitivity analyses using a reduced variable set derived from significant factors in the univariable analysis. Age, recipient sex, and conditioning regimen, which were significantly associated with NRM in univariate analysis, were entered into these models. Even with this approach, the CHARM score remained unassociated with NRM (HR: 1.37, 95% CI: 0.81-2.31,  $p=0.230$ ). As outlined in the limitations section of our study [1], the relatively low proportion of older patients in our cohort likely contributed to the absence of a significant association between the CHARM score and NRM.

Overall, our findings suggest that, in unrelated single-unit CBT, the CHARM score appears more closely associated with relapse and overall survival than with NRM. We agree that further validation with larger, multi-center cohorts will be essential to better define the prognostic utility of the CHARM score in this specific setting. We sincerely appreciate the valuable comments from Yang and Liu, which help to further contextualize and strengthen the interpretation of our results.

Sincerely,

Seiko Kato, Takaaki Konuma

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