



Impact of HLA-DPB1 and DPA1~DPB1 linkage mismatch on survival in HLA-14/14 matched unrelated donor HSCT: establishment and clinical validation of a predictive model based on NGS technology

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Aim

While HLA-DPB1 mismatches significantly influence unrelated donor hematopoietic stem cell transplantation (URD-HSCT) outcomes, the role of HLA-DPA1~DPB1 linkage mismatches remains unclear. This study evaluates their clinical impact and establishes a predictive model to optimize donor selection.

Methods and Materials

A retrospective study was conducted on 250 HLA-14/14 matched URD-HSCT cases at the First Affiliated Hospital of Soochow University from January 2016 to September 2021. Follow-up was conducted until December 31, 2021. HLA typing was performed using NGS for HLA-A, -B, -C, -DRB1, -DQB1, -DQA1, -DRB3/4/5, -DPA1, and -DPB1 typing. HLA-DPA1 and DPB1 mismatches were categorized according to α -chain mismatch only, β -chain mismatch only, and complete molecule mismatch (α + β -chain), and their impact on two-year overall survival (OS) and non-relapse mortality (NRM) was evaluated.

A DPA1~DPB1 linkage prediction model was developed using an artificial neural network algorithm, and with reference to the amino acid FASTA data of HLA-DPA1 and DPB1 of all known sequences published by IPD-IMGT/HLA. The model was validated using clinical and follow-up data from 250 donor-recipient pairs.

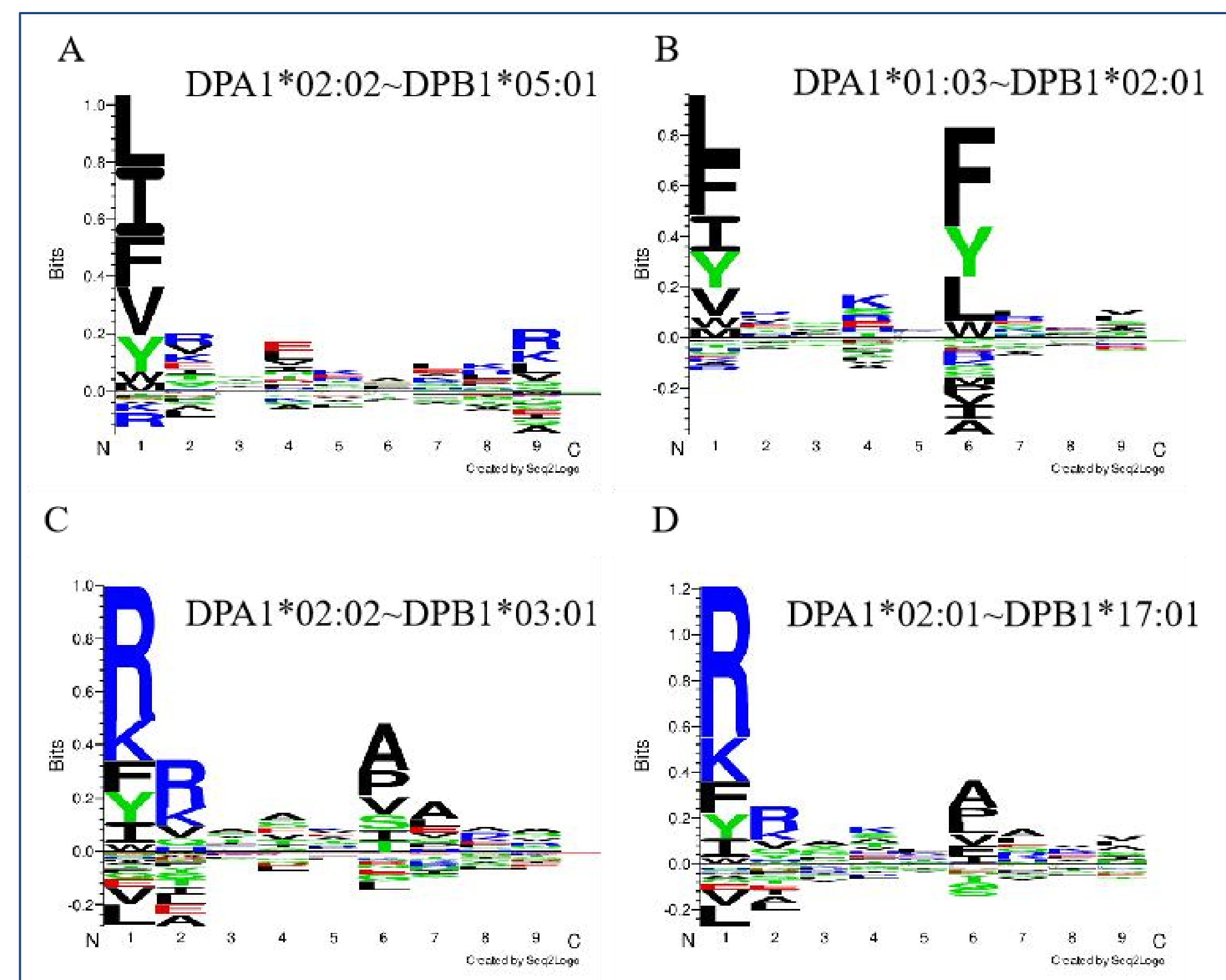


Figure 2. Examples of the DPA1~DPB1 linkage prediction model and the most representative pattern. Panel A illustrates an example of the Type I pattern, with the most representative DPA1*02:02~DPB1*05:01. Panel B displays the Type II hydrophobic pattern. Panel C shows the Type III amphipathic pattern, and Panel D represents the Type IV hydrophilic pattern.

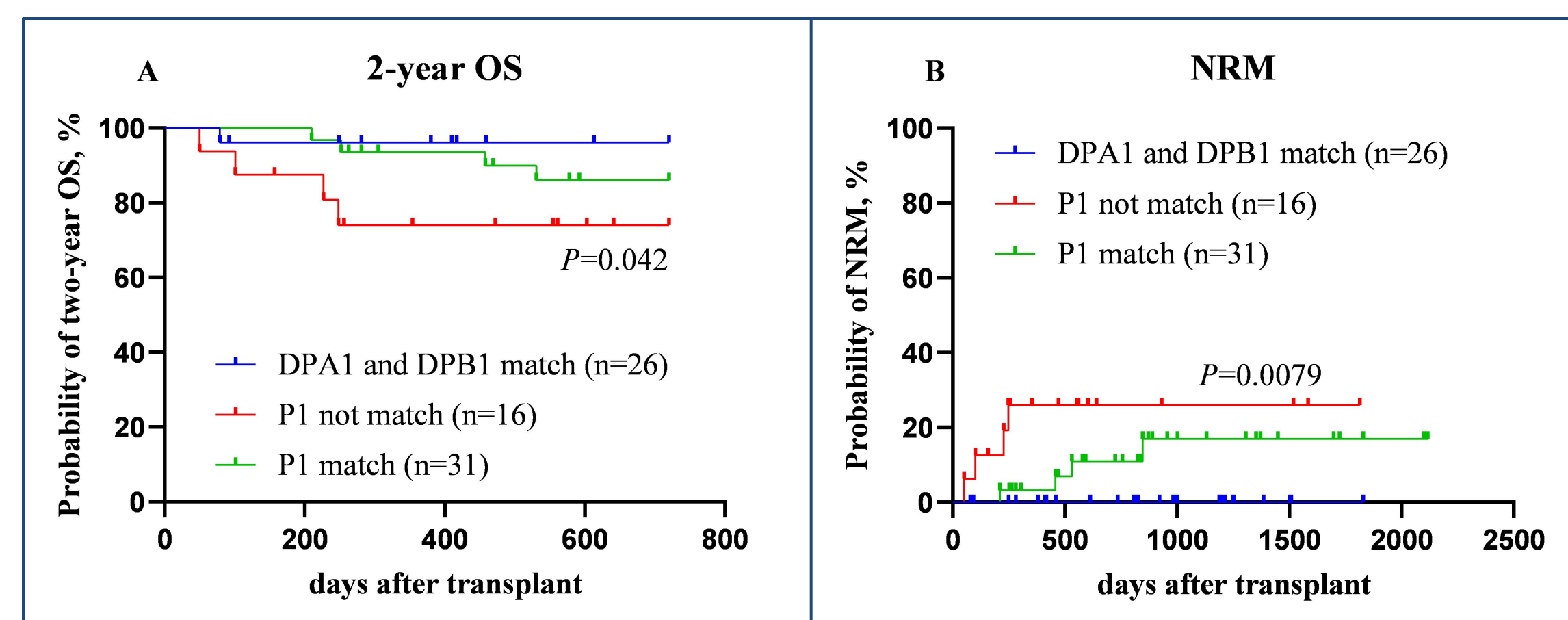


Figure 3. Prediction model showed that mismatches in hydrophobicity/hydrophilicity at the HLA-DP peptide P1 region between donor and recipient significantly impact 2-year OS and NRM after transplantation. Compared to the fully HLA-DPA1 and DPB1 matched group, the "P1 not match" group showed a statistically significant decrease in 2-year OS (A) and increase in NRM (B).

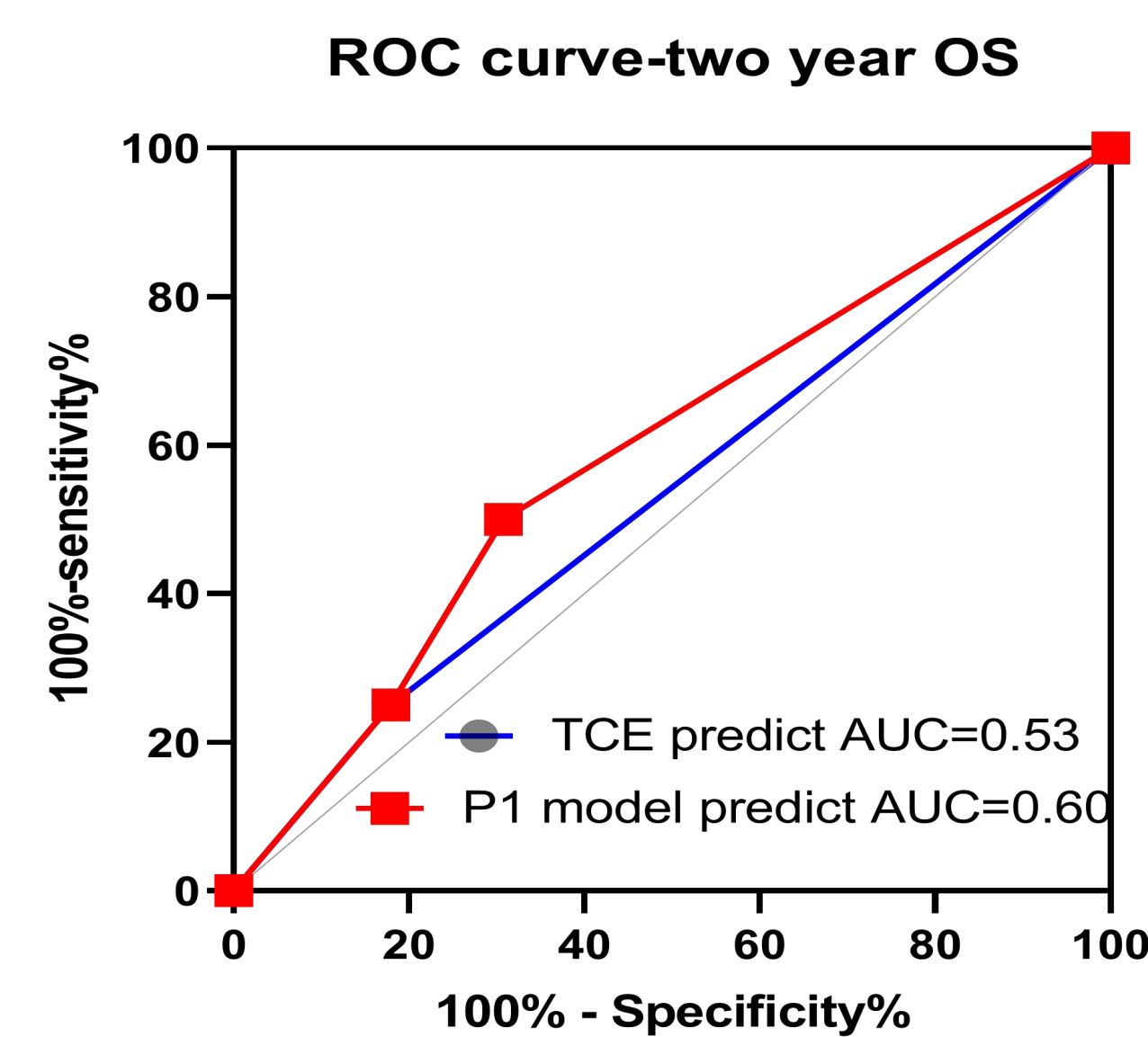


Figure 4. Comparison of the area under the curve (AUC) of the DPA1~DPB1 linkage predictive model and the DPB1 TCE model for Predicting 2-year OS after Transplantation.

Results

DPA1 and DPB1 match/mismatch analysis

Only 10.4% (26/250) of cases had matched DPA1 and DPB1 alleles. The remaining 89.6% of donors and recipients demonstrated DPA1 or DPB1 mismatch. Of these, the proportion with DPB1 alleles mismatched was 18.8% (47/250) and 70.0% (175/250) had both DPA1 and DPB1 alleles mismatched. DPA1 alleles mismatched and DPB1 alleles matched was 0.8% (2/250).

DPB1 locus-specific and DPA1~DPB1 linkage mismatches

Among cases with mismatches, we identified three key findings. For allele-specific effects, prevalent DPB1 allelic mismatches, such as DPB1*02:01/DPB1*03:01, were associated with decreased 2-year OS and increased NRM, while DPB1*02:02/DPB1*05:01 and DPB1*02:01/DPB1*05:01 mismatches had no significant impact. For DPA1-DPB1 linkage patterns, high-risk DPA1*02:02-DPB1*05:01/DPA1*02:01-DPB1*17:01 mismatch decreased 2-year OS, especially in AML/MDS recipients, while DPA1*02:02-DPB1*05:01/ DPA1*01:03-DPB1*02:01 mismatch showed no impact on outcomes.

Establishment and validation of linkage prediction model

We established 47 types of DPA1-DPB1 linkage prediction models and categorized them into four types (Types I-IV) based on amino acid hydrophilic and hydrophobic properties in the anchoring position of peptides P1 to P9. Patients with P1 mismatches with donors had lower 2-year OS and higher NRM compared to fully matched cases, whereas there was no significant difference in the 2-year OS rate and NRM rate in P1 match patients. The predictive model outperformed the TCE model in predicting 2-year OS, with a larger area under the ROC curve (0.60 vs. 0.53).

Conclusions

HLA DPA1-DPB1 linkage mismatches significantly impact URD-HSCT outcomes, with specific allelic pairs and structural features predicting survival and NRM. Our neural network model provides superior donor selection guidance compared to TCE, emphasizing the importance for comprehensive HLA-DP assessment in transplantation strategies.

HLA-DP Mismatch Impact at Three Structural Levels

Single center Study | 250 HLA 14/14 Matched Donor-Recipient Pairs | 70% Concurrent DPA1 and DPB1 Mismatches

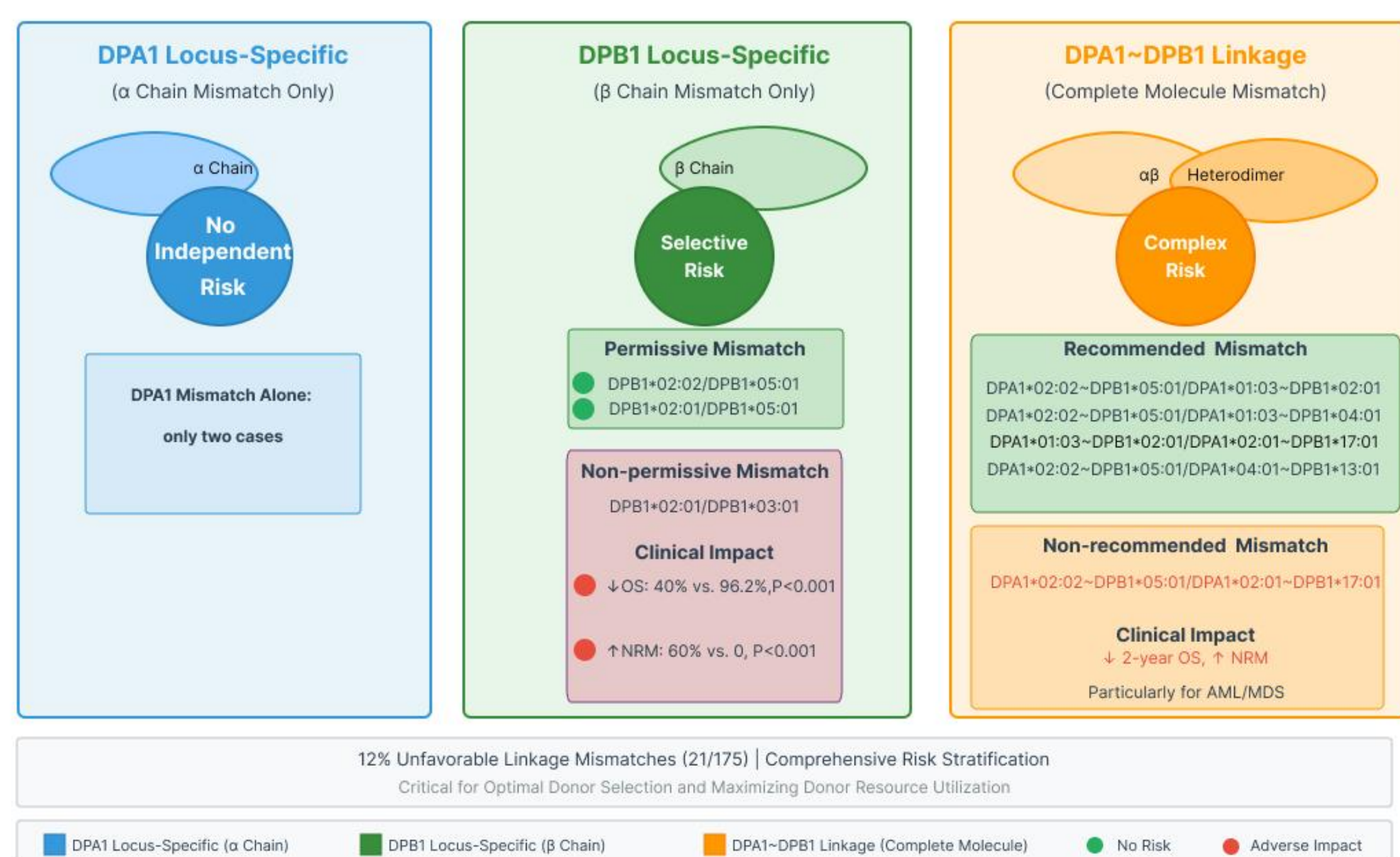


Figure 1. The flowchart of the HLA-DPA1 and DPB1 locus-specific mismatch analysis, the HLA-DPA1~DPB1 linkage mismatch analysis methodology, and the key observational findings from this single-center study.

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