Anti-HLA antibody signatures provide a new tool for early diagnostics of acute graft rejection after renal transplantation

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INTRODUCTION

Molecules of the human leukocyte antigen (HLA) system expressed on donor cells present the major barrier to acceptance of kidney transplants. The presence of serum anti-HLA antibodies is associated with acute antibody mediated transplant rejection and compromised long term outcome. Studies showed that anti-HLA antibodies often precede transplant rejection, but not all patients with antibodies encounter rejection or subsequent graft loss. Early detection of HLA antibodies predictive of rejection could help prevent imminent graft rejection and improve long-term outcome.

AIMS AND OBJECTIVES

The aim is to uncover a HLA antibody pattern predictive of acute rejection early after kidney transplantation. Serum HLA antibody signature of rejection and no-rejection renal transplant recipients will be defined to determine the clinical relevance of HLA antibodies present before and early after transplantation.

METHOD

Kidney transplant recipients enrolled in a large multicenter clinical trial (HARMONY) with a follow up of one year were included in the study. Serum samples obtained pre- and post-transplantation were screened for HLA antibodies using LABScreen mixed beads (One Lambda, CanogaPArk, CA, USA). Identification of HLA antibodies for HLA positive patients was performed using Single Antigen Beads (OneLambda). Data evaluation was performed using Fusion HLA software (Version 3.3., LABScreen, One Lambda). Raw data was analysed using machine learning and feature selection methods.

RESULTS

Kidney transplant recipients were monitored for acute rejection events in the first year after transplantation. 77 patients with acute T-cell rejections were chosen as the rejection group, 80 patients with similar demographic characteristics were selected as the control group.

Fig. 1: Patients were divided in two groups based on the incidence of rejection events within the first year post-transplant. Up to three samples per patients were available taken pre- and at week 2 and month 3 post-transplantation. For the rejection group, post-transplant samples were subdivided based on the time point of the first rejection.

Screening for serum antibodies revealed that the incidence of HLA antibodies was higher in the rejection group, 52% of rejection group patients were HLA antibody positive at least for one of the tested time points compared to 30% of control patients (p<0.01).

The prevalence of HLA antibodies in pre-transplant samples was higher for patients suffering rejection within the first 12 months post-transplantation, with 24% of the control and 37% of rejection groups patients having HLA antibodies before receiving the graft. This difference however was not statistically significant and therefor not sufficient for prediction of rejection.
Prevalence of HLA antibodies was also similar in post-transplant samples taken before a rejection and control patient samples taken at the same time point after transplantation. The only statistically significant difference we could find was by comparing post-rejection samples taken at week 2 post-transplant with control samples taken at the same time.
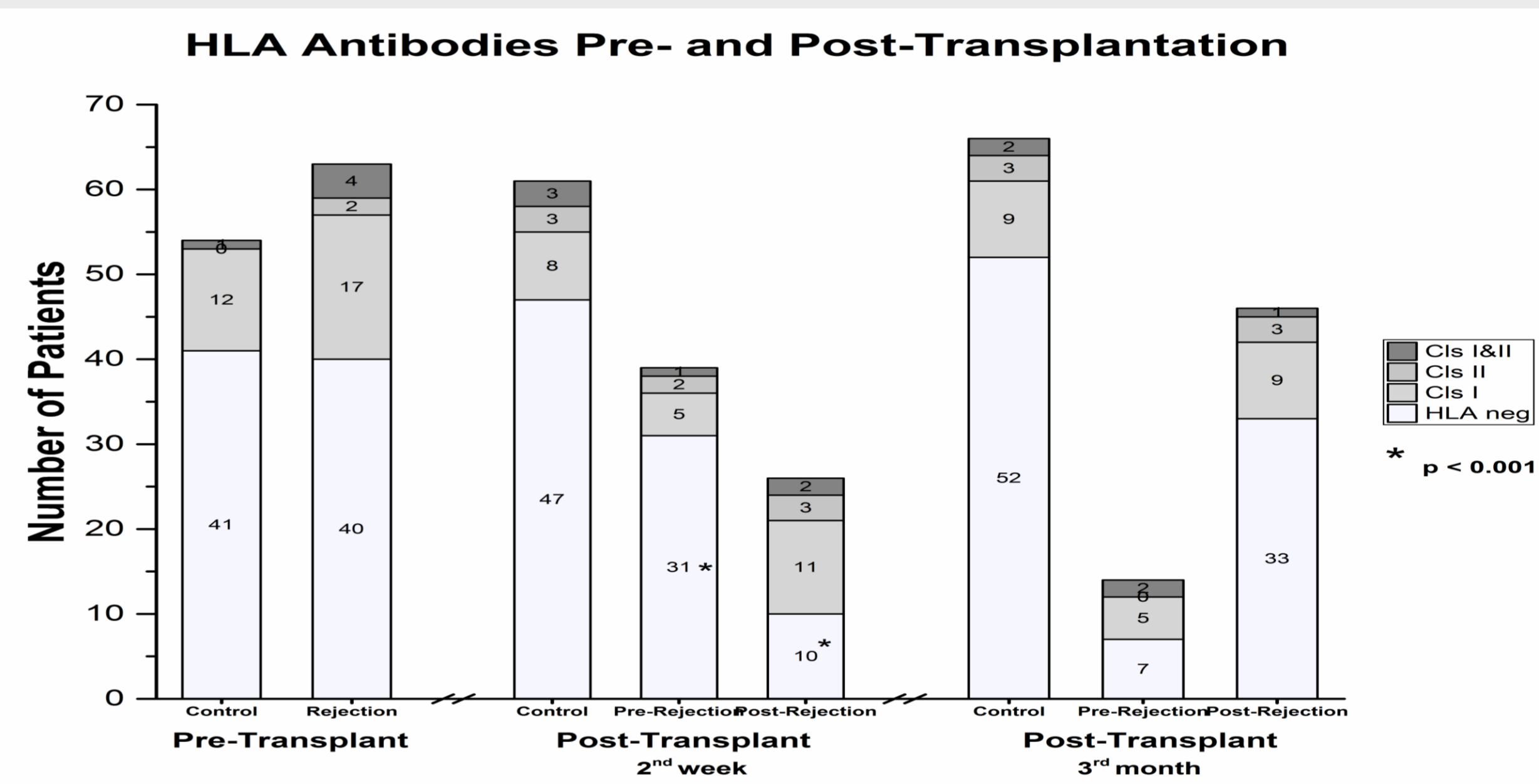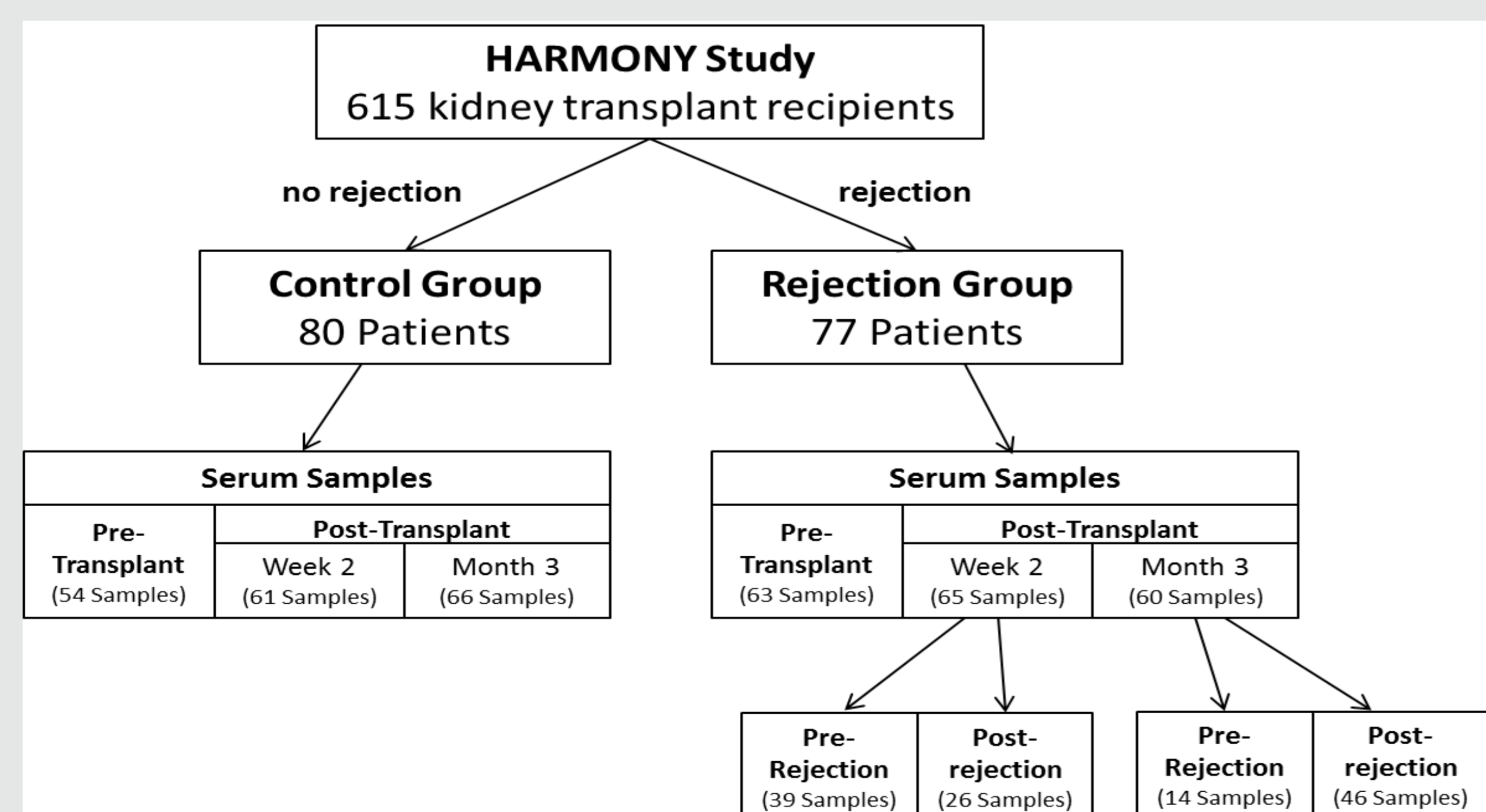

Fig. 2: Comparison of control and rejection group samples at different time points pre- and post-rejection provided no information on imminent rejection events. The incidence of HLA antibodies was only statistically different after the rejection occurred.

Moreover raw HLA antibody data was evaluated using machine learning and feature selection methods. Potential Support Vector Machine (P-SVM) classification run on rank-transformed MFI data was able to find HLA signatures in pre-transplant HLA data highly predictive of rejection (p<0.02) with a balanced predictive accuracy of about 63%.

For HLA positive patients pre-transplant sera was further evaluated using Single Antigen beads to identify antibody serotypes. HLA serotyp data obtained from the fusion HLA software and raw HLA serotyp data were again classified using P-SVM. While both classifications succeded in extracting significant, discriminative features associated with rejection using raw data yielded a higher BACC of 81% compared to categorical data obtained from the fusion software with a BACC of 71%.

CONCLUSION AND OUTLOOK

Preliminary data analysis suggest that raw HLA antibody signature data has the potential to become a novel diagnostics tool for early, pre-transplant assessment of risk of graft rejection.

ACKNOLEDGEMENT