

# Estimating the probability of positive crossmatch after negative virtual crossmatch

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*Abbreviations:* PRA (panel reactive antibodies), HLA (human leukocyte antigen), CDC (complement dependent cytotoxicity, CDF (cumulative distribution function)

## Abstract

This paper estimates the probability of virtual crossmatch failure in kidney exchange matching. In particular, the probability of a positive crossmatch after a negative virtual crossmatch is related to the recipient's PRA level. Using Dutch kidney exchange data, we find significant evidence that this probability increases non-linearly with PRA level. We estimate a probit model that describes this relationship.

## Introduction

Living donor kidney transplantation is the preferred treatment for patients with end-stage renal disease. However, due to blood type and crossmatch incompatibility over 40 percent of living donors are incompatible with their intended recipient. Kidney exchange identifies matches between such incompatible donor-recipient pairs that allow them to proceed with transplantation through a cyclic transplant procedure (1) (2) (3) (4) (5) (6) (7) (8). In order to determine these matches, compatibility between all patients and donors is usually analyzed by testing blood type compatibility and by performing a virtual crossmatch. Then, after a set of desirable transplant procedures is identified by a specialized computer algorithm, actual crossmatches are performed for all selected recipient-donor combinations. If any of the actual crossmatches is positive, the computer algorithm is rerun with the updated compatibility structure, and the process is repeated until a feasible set of transplants is established.

The number of positive crossmatches after a negative virtual crossmatch can be substantial, with figures up to 90 % of the performed crossmatches being reported in the US. In this research we estimate the probability of positive crossmatch after a negative virtual crossmatch on an individual level, using Dutch clinical data. In particular, we relate the probability to the recipient's sensitization level as captured in the recipient's PRA score with respect to the kidney exchange donor population.

## Methods

### *Data*

This study uses empirical data from the registry of the Dutch national kidney exchange program. The available data include 438 ABO blood type or crossmatch incompatible patient-donor pairs who participat-

ed in Dutch kidney exchanges between October 2003 and January 2011, as well as outcomes of 331 crossmatch tests performed by the national reference laboratory for histocompatibility testing in Leiden. The data contain blood types of all patients and donors as well as center-reported patient PRA values at time of entry and, if available, at time of transplantation. Donor HLA types and recipient unacceptable HLA mismatches are also included. The national reference laboratory identifies unacceptable HLA specificities on basis of a combination of a complement dependent cytotoxicity (CDC) and a solid phase antibody screening. Antibody specificities leading to a positive CDC crossmatch are considered to be a contraindication for transplantation and the HLA antigens recognized are defined as unacceptable mismatches.

### **Kidney exchange donor population based PRA levels**

Because center-reported PRA levels are based on the general population, they may not accurately reflect the difficulty of finding compatible donors in the kidney exchange program. For that reason additional kidney exchange donor population PRA levels are computed based on virtual crossmatches between each patient and all donors in the data set. Throughout the rest of this paper, whenever we refer to a PRA level, we refer to these kidney exchange donor population based PRA levels. Table 1 details the patient and donor characteristics.

**Table 1: Patient and donor characteristics**

	ABO blood type			
	A	B	AB	O
Patients (%)	30	15	1	54
Donors (%)	56	14	2	29
	PRA level w.r.t. general population (at time of entry)			
	0-9	10-79	80-100	
Patients (%)	78	17	5	
	PRA level w.r.t. kidney exchange donor population			
	0-9	10-79	80-100	
Patients (%)	48	35	17	

### ***Relating the probability of positive crossmatch to PRA level***

Table 2 displays the number of positive crossmatch outcomes for each of the PRA level categories of Table 1. The numbers clearly indicate that there is a relationship between the probability of a positive crossmatch after a negative virtual crossmatch and the PRA level.

**Table 2: Relation between positive crossmatch and PRA level**

	PRA level w.r.t. kidney exchange donor population		
	0-9	10-79	80-100
# Crossmatches	126	173	32
Positive (%)	6	31	44

However, the crossmatch tests reported in Table 2 are not all independent. Regularly, multiple crossmatch tests correspond to an individual patient. Multiple tests might, for example, be required when a patient's initial test is positive, or when a patient's crossmatch test is negative but the proposed transplant procedure cannot take place because of a positive crossmatch for another patient involved in the procedure. We need to investigate the effects and significance of this dependence relation before making inferences.

### Pearson's $\chi^2$ test for independence

Let  $T_{i,j}$  denote the outcome of the  $i$ -th crossmatch test for recipient  $j$ , that is  $T_{i,j} = 1$  if the crossmatch is positive, and  $T_{i,j} = 0$  otherwise. Furthermore, let  $PRA_j$  denote recipient  $j$ 's PRA level. We are interested in estimating

$$\Pr[T_{i,j} = 1: PRA_j, T_{i-1,j}, \dots, T_{1,j}]$$

In order to assess whether the tests  $T_{i-1,j}, \dots, T_{1,j}$  significantly affect this probability, we perform a test of independence using Pearson's  $\chi^2$  test statistic. Let  $O_{i,J}^+ := \sum_{j \in J} T_{i,j}$  and  $O_{i,J}^- := \sum_{j \in J} 1 - T_{i,j}$  denote the observed number of patients in PRA category  $J$  with, respectively, a positive and a negative  $i$ -th test. If there are a total of  $n$  observations, at most  $m$  tests per recipient, and  $p$  PRA categories, then, under the null hypothesis of statistical independence, we have

$$E_{i,J}^+ := \frac{(O_{i,J}^+ + O_{i,J}^-) \cdot \sum_{k=1}^m O_{k,J}^+}{n}$$

and

$$E_{i,J}^- := \frac{(O_{i,J}^+ + O_{i,J}^-) \cdot \sum_{k=1}^m O_{k,J}^-}{n}$$

The test statistic is then given by

$$\chi^2 = \sum_J \frac{(O_{i,J}^+ - E_{i,J}^+)^2}{E_{i,J}^+} + \sum_J \frac{(O_{i,J}^- - E_{i,J}^-)^2}{E_{i,J}^-}$$

and follows a  $\chi^2$ -distribution with  $p - 1$  degrees of freedom.

### Probit regression

In order to estimate the probability of positive crossmatch after a negative virtual crossmatch on an individual level, we use a probit regression model. In this approach, the probabilities are modeled as

$$\Pr[y_i = 1: X] = \Phi(X^T \beta)$$

where  $y_i$ ,  $i = 1, \dots, n$ , denotes the  $i$ -th observed crossmatch test,  $X$  is a vector of  $k$  regressors,  $\beta$  is a vector of regression parameters and  $\Phi$  is the cumulative distribution function (CDF) of the standard normal distribution. The parameters  $\beta$  are estimated by the maximum likelihood estimator  $\hat{\beta}$  as follows:

$$\hat{\beta} = \operatorname{argmax}\{\ln(L(\beta: X))\}$$

where  $\ln(L(\beta: X))$  is the log-likelihood function defined by

$$\ln(L(\beta: X)) = \sum_{i=1}^n \left( y_i \ln \Phi(x_i^T \beta) + (1 - y_i) \ln(1 - \Phi(x_i^T \beta)) \right)$$

To diagnose the quality of the regression, we perform several tests. The first is the likelihood-ratio test, which tests if the deviance statistic  $D$ , as defined below, deviates significantly from zero:

$$D = -2 \ln \left( \frac{L(\hat{\beta}: X)}{L(\hat{\beta}_0: C)} \right)$$

where  $C$  is a vector of ones, and  $\hat{\beta}_0 = \operatorname{argmax}\{\ln(L(\beta_0: C))\}$ .  $D$  follows a  $\chi^2$ -distribution with  $k - 1$  degrees of freedom and if it differs significantly from zero, it indicates a good fit of the model.

The next statistic for determining goodness of fit is McFadden's  $R^2$ , which is computed as

$$R^2 = 1 - \frac{\ln(L(\hat{\beta}: X))}{\ln(L(\hat{\beta}_0: C))}$$

and lies between 0 and 1. Higher values of  $R^2$  correspond to a relatively higher overall significance of the model.

Finally, we perform a Lagrange Multiplier (LM) test on heteroskedasticity of the form

$$\Pr[y_i = 1: X] = \Pr[\varepsilon_i \leq X^T \beta], \varepsilon_i \sim N(0, \sigma_i)$$

with

$$\sigma_i = e^{z_i^T \gamma}$$

where  $z_i$  is a vector of observed variables, and  $\gamma$  is a vector of regression parameters. The LM test is performed by taking the standardized residuals  $e_i^*$  from the homoskedastic model, regressing these on the gradient of the heteroskedastic model using ordinary least squares, and then computing

$$LM = n \frac{\sum_{i=1}^n (\hat{e}_i^*)^2}{\sum_{i=1}^n (e_i^*)^2}$$

where  $\hat{e}_i^*$  denote the fitted values of the secondary regression. Under the null hypothesis of homoskedasticity,  $LM \sim \chi^2(g)$  where  $g$  is the number of parameters in  $\gamma$ .

## Results

Table 3 shows the outcomes of a  $\chi^2$  test for independence of the probability of a positive crossmatch test and the outcomes of previous tests, per PRA category as in Table 1. For each of the PRA categories, there is no significant evidence to reject the null hypothesis of independence. Therefore all the observed

crossmatch results can be straightforwardly used to estimate the probability of a positive crossmatch within each PRA category, as was done in Table 2.

**Table 3:** Test for independence

		Test 1	Test 2	Test 3	Test 4	Test 5	Test 6	Test 7	Total
PRA 0-9	Positives	4	2	1	0				7
	Negatives	79	31	8	1				119
	Total	83	33	9	1				126
	$\chi^2 = 0.69$	P = 0.124							
PRA 10-79	Positives	23	16	8	3	2	1	0	53
	Negatives	66	26	17	4	3	2	2	120
	Total	89	42	25	7	5	3	2	173
	$\chi^2 = 3.67$	P = 0.280							
PRA 80-100	Positives	8	3	2	1	0			14
	Negatives	11	5	1	0	1			18
	Total	19	8	3	1	1			32
	$\chi^2 = 2.85$	P = 0.417							

Table 4 shows the outcomes of a probit regression of the latent individual probability of a positive crossmatch on PRA. The coefficient of PRA is highly significant, as is the likelihood-ratio test for model fit. Figure 1 shows a plot of the fitted probabilities. The non-linear relationship between the probability of a positive crossmatch and the PRA level is clearly visible. To assess whether this relationship is correctly modeled, we further diagnose a plot of the standardized residuals (Figure 2). The standardized residuals behave nicely overall, showing only weak signs of heteroskedasticity for PRA values close to 0 and 100. This indicates that possibly the tails of the normal distribution do not correctly fit the distribution of the probabilities. However, a formal Lagrange Multiplier test reveals that the amount of heteroskedasticity is not significant (Table 4). It therefore appears that

$$\Pr[T_{i,j} = 1: PRA_j] = \Phi(-1.5007 + 0.0170 \cdot PRA_j)$$

appropriately models the individual probability of a positive crossmatch.

**Table 4:** Probit regression

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-1.5007	0.1486	-10.1007	<0.0001
PRA	0.0170	0.0026	6.5340	<0.0001
Deviance	304.5770	Prob (Deviance)		<0.0001
LM-test	1.7514	Prob (LM-test)		0.1857
McFadden's R-squared	0.1342			

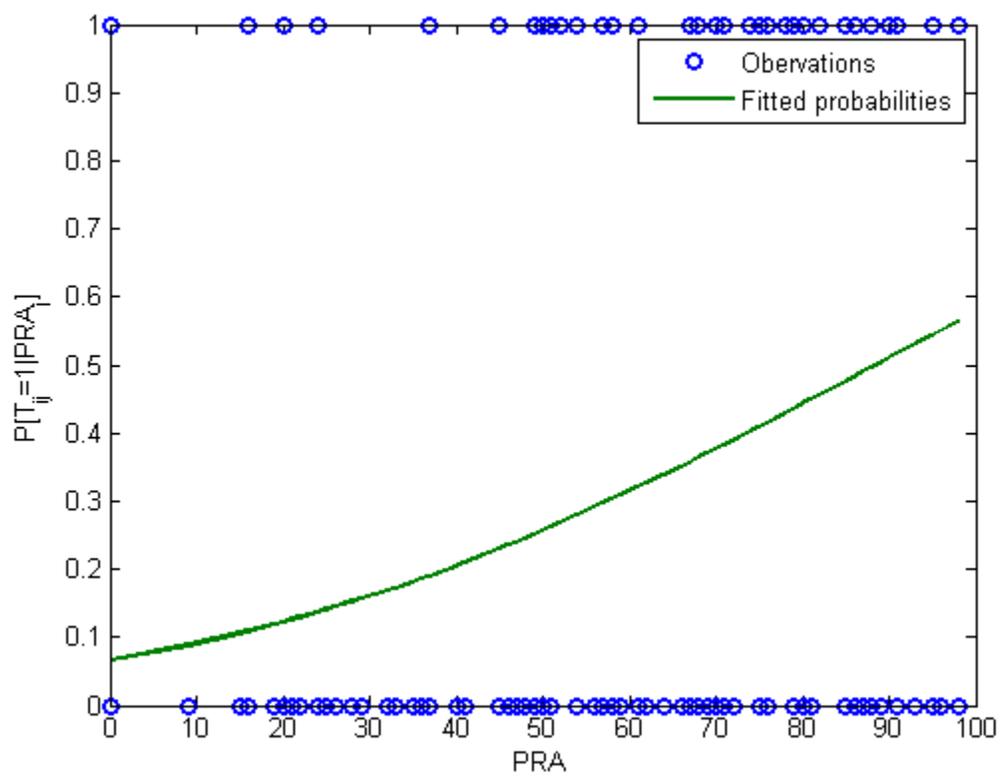


Figure 1 Fitted probabilities

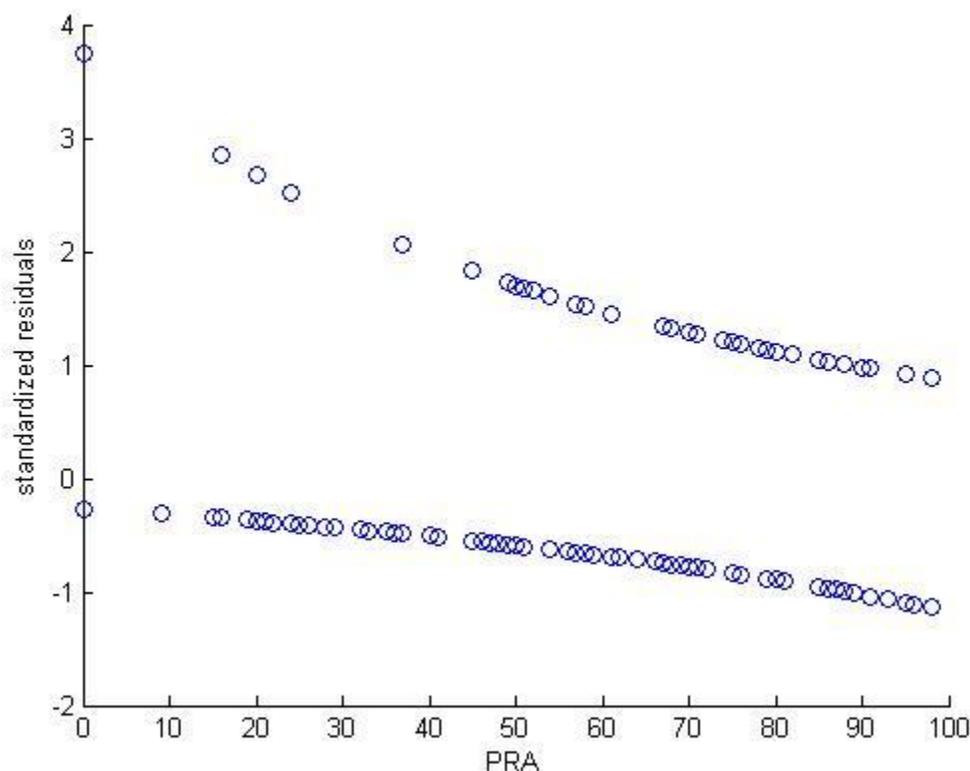


Figure 2 Standardized residuals versus PRA

## Discussion

In this paper we have estimated the probability of virtual crossmatch failure in kidney exchange matching by relating this probability to the recipient's PRA level. Our findings indicate that the non-linear relationship between the PRA level and the probability of virtual crossmatch failure is modeled appropriately by a homoskedastic probit model.

Although this model improves on the estimations made in previous literature (e.g. (9)), we do not claim that the PRA level is the sole explanatory factor for virtual crossmatch failures, nor that virtual crossmatch failure is the only cause of failure preventing kidney exchange matches from going forward to transplantation. There may be other factors which play a role, such as recipient health status and likelihood of withdrawal of incompatible donors, but their impact will likely be smaller than the impact of the PRA level, and as we did not have data available on these other factors, they were not explicitly included in this research. Instead, these exogenous factors are captured by the constant terms in our model.

Additionally, our findings are conditional to our assumptions (although we applied multiple statistical test to verify these assumptions) and to our data (although comparison of our data (see Table 3) with the data used in related literature (see Table 2 in (9)) suggests failure rates are comparable).

Considering the practical impact of failure of kidney exchange matches, particularly due to failure of virtual crossmatching, we hope the present paper may serve to improve kidney exchange simulations by taking into account virtual crossmatch failure more accurately, and thereby help policy makers select the best kidney exchange mechanisms.

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